

Addenda from the December 2022 PBAC Intracycle, March 2023 and July 2023 PBAC Meetings have been included at the end of this Public Summary Document (PSD).

5.14 TRASTUZUMAB DERUXTECAN, Powder for I.V. infusion 100 mg, Enhertu[®], AstraZeneca Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested a Category 1, Section 100, Authority Required listing for trastuzumab deruxtecan (T-DXd; Enhertu[®]) for the treatment of human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer (mBC) for patients who have progressed following a prior HER2 directed therapy in the metastatic setting or relapsed during or within 6 months of receiving a HER2 directed therapy in the adjuvant setting.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus trastuzumab emtansine (T-DM1; Kadcyla[®]) (Table 1).

Table 1: Key components of the clinical issue addressed by the submission.

Component	Description
Population	Adult patients with metastatic HER2-positive breast cancer who have received prior treatment with a HER2-directed regimen in the metastatic setting or have progressed within 6 months of receiving adjuvant HER2 directed treatment.
Intervention	Trastuzumab deruxtecan (T-DXd; ENHERTU) 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21 day cycle) until disease progression
Comparator	Trastuzumab emtansine (T-DM1) 3.6 mg/kg given as an intravenous infusion once every 3 weeks (21 day cycle) until disease progression
Outcomes	PFS, OS, DoR, ORR, QoL and safety
Clinical claim	T-DXd demonstrates superior efficacy and non-inferior safety in patients with HER2 positive metastatic breast cancer (mBC) who have received prior treatment with at least one HER2-directed regimen in the metastatic setting, compared to T-DM1

Source: Table 1.2, p10 of the submission.

HER2 = human epidermal growth factor receptor 2; DoR = duration of response; mg/kg = milligrams per kilogram; PFS = progression free survival; OS = overall survival; ORR = objective response rate; QoL = quality of life; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

2 Background

Registration status

- 2.1 The submission was lodged under the TGA/PBAC Parallel Process. The Sponsor submitted an application for marketing authorisation (transition from provisional to full registration) to the TGA in November 2021, for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a prior anti-HER2-based regimen. The application was identified for consideration under the

United States Food and Drug Administration's (FDA) Project Orbis. TGA-specific evaluation reports will not be issued for this submission. While the timing of the FDA Assessment is unknown, the TGA Delegate's Overview was available prior to the July 2022 PBAC meeting.

3 Requested listing.

- 3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRASTUZUMAB DERUXTECAN Injection	NEW (Public) NEW (Private)	675 mg	08
Available brands			
Enhertu® Trastuzumab deruxtecan 100 mg injection, 1 vial			

Restriction Summary / Treatment of Concept:
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒ Medical Practitioners
Restriction type: ☒ Authority Required (<i>telephone/online PBS Authorities system in writing only via post/HPOS upload</i>)
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
Administrative Advice: Increased maximum amounts can be requested where a patient's weight is greater than 125 kg.
Administrative Advice: Special Pricing Arrangements apply.
Episodicity: [blank]
Severity: Metastatic (<i>Stage IV</i>)
Condition: Stage IV metastatic HER2+ <i>positive</i> breast cancer
Indication: Metastatic stage IV Metastatic (<i>Stage IV</i>) HER2+ <i>positive</i> breast cancer
Treatment Phase: Initial <i>treatment</i>
Clinical criteria:
Patient must have evidence of human epidermal growth factor (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) either in the primary tumour or a metastatic lesion
AND
Clinical criteria:
The condition must have progressed following treatment with at least one prior HER2 directed regimens for metastatic breast cancer
OR
Clinical criteria:
The condition must have progressed during or within 6 months following adjuvant treatment with a HER2 directed therapy
AND

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

Clinical criteria:
Patient must have a WHO performance of 0 or 1
AND
Clinical criteria:
Patient must not have received <i>prior treatment with this drug for this condition</i> this drug for this indication
AND
Clinical Treatment criteria:
The treatment must be as monotherapy
AND
Treatment criteria:
The treatment must be the sole PBS subsidised treatment for this condition
Clinical Population criteria:
The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 4550% and/or with symptomatic heart failure.
Prescribing Instructions: <i>Authority applications for initial treatment must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail and must include:</i> (i) details (date, unique identifying number/code or provider number) of the pathology report from an Approved Pathology Authority confirming evidence of HER2 gene amplification in the primary tumour or a metastatic lesion by in situ hybridisation (ISH); and (ii) details of the last treatment with HER2 regimen including the medicine name(s), date and total number of cycles; AND (iii) for disease progression following adjuvant therapy, the date of demonstration of progression during or within 6 months of completing treatment with HER2 therapy. <i>If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, please provide details of the degree of this toxicity at the time of application.</i> <i>All reports must be documented in the patient's medical records.</i>
Prescribing Instructions: <i>If the application is submitted through HPOS upload or mail, it must include:</i> (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)
Prescribing Instructions: <i>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval.</i>
Administrative Advice: <i>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</i> <i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au.</i> <i>Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS).</i> <i>Applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos.</i> <i>Or mailed to:</i>

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& July 2023 Addenda*

Services Australia
Complex Drugs
Reply Paid 9826
HOBART TAS 7001

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRASTUZUMAB DERUXTECAN Injection	NEW (Public) NEW (Private)	675 mg	8
Available brands			
Enhertu® Trastuzumab deruxtecan 100 mg injection, 1 vial			

Restriction Summary / Treatment of Concept:
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒ Medical Practitioners
Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Increased maximum amounts can be requested where a patient's weight is greater than 125 kg.
Administrative Advice: Special Pricing Arrangements apply.
Episodicity: [blank]
Severity: Metastatic (Stage IV)
Condition: Stage IV metastatic HER2+positive breast cancer
Indication: Metastatic stage IV Metastatic (Stage IV) HER2+positive breast cancer
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for metastatic (Stage IV) HER2 positive breast cancer
AND
Clinical criteria:
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
AND
Clinical criteria:
Patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug
Clinical Treatment criteria:
The treatment must be as monotherapy
AND
Clinical Population criteria:

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure.
AND
Population criteria:
The treatment must not exceed a lifetime total of one continuous course for this PBS indication.
Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
Prescribing Instructions: The treatment must not exceed a lifetime total of one continuous course for this PBS indication.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRASTUZUMAB DERUXTECAN Injection	NEW (Public) NEW (Private)	675 mg	8
Available brands			
Enhertu® Trastuzumab deruxtecan 100 mg injection, 1 vial			

Restriction Summary / Treatment of Concept:
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒ Medical Practitioners
Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Increased maximum amounts can be requested where a patient's weight is greater than 125 kg.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria.
Episodicity: [blank]
Severity: Metastatic (Stage IV)
Condition: Stage IV metastatic HER2+positive breast cancer
Indication: Metastatic stage IV Metastatic (Stage IV) HER2+positive breast cancer
Treatment Phase: Grandfathering Transitioning from non-PBS to PBS-subsidised treatment – Grandfather arrangements
Clinical criteria:
Patient must have stable or responding disease.
AND
Clinical Treatment criteria:
The patient must have received non-PBS-subsidised treatment with this drug for metastatic (Stage IV) HER2 positive breast cancer prior to [DATE of PBS listing]
AND

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

Clinical Treatment criteria:
The treatment must be the sole PBS subsidised treatment for this condition. <i>The treatment must be as monotherapy</i>
AND
Clinical Population criteria:
The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 4550% and/or with symptomatic heart failure.
Administrative Advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>

- 3.2 The submission proposed initial, continuing and grandfathering treatment criteria. A special pricing arrangement was proposed in the submission.
- 3.3 The proposed restrictions are similar to the PBS restrictions for the nominated comparator T-DM1 (see paragraph 5.1 below), with the exception that the prior HER2 directed therapies have not been specified in the proposed restrictions; for T-DM1, prior therapies are specified as pertuzumab and trastuzumab in combination, or adjuvant trastuzumab for patients who have progressed during or within 6 months of therapy. The ESC noted that the DB01 trial specified that patients must have received prior treatment with trastuzumab and a taxane.
- 3.4 The proposed restriction allows T-DXd therapy for treatment in the metastatic setting as first-line therapy (for patients who have had a relapse during or within 6 months of adjuvant HER2 directed treatment), second-line therapy (for patients whose disease has progressed following treatment with one HER2-directed regimen), or third- or later-line therapy (for patients who have received more than one regimen in the metastatic setting including at least one HER2-directed regimen).
- 3.5 While the proposed restriction was similar to the inclusion criteria used in the key trial (DB03), there were some differences, as follows:
- The proposed restriction did not include patients with unresectable locally advanced disease, although the DB03 trial included this population and ‘unresectable’ patients are included in the requested TGA indication (paragraph 2.1). The submission did not justify why these patients were excluded, and the ESC commented that it would be reasonable to include these patients. The Pre-Sub-Committee Response (PSCR) and ESC noted that the financial estimates do not include this population.
 - The proposed restriction included patients with rapid relapse during or within 6 months of adjuvant treatment with a HER2 directed therapy; this includes patients who received adjuvant trastuzumab or T-DM1. The latter population was excluded from the DB03 trial as they could not ethically be randomised to another line of T-DM1. The PBAC noted that this patient group represents a small percentage of HER2 positive breast cancer patients who remain at high risk of a

recurrence, and therefore advised a restriction including this patient population was reasonable.

- 3.6 The PBAC noted that the proposed restriction type for the initial phase of treatment was 'Authority Required – In Writing'. It advised that a restriction type of 'Authority Required (telephone/online PBS Authorities system)' was more appropriate for both the initial and continuing phases of T-DXd therapy and is in line with the restriction type of the nominated comparator, T-DM1.

For more detail on PBAC's view, see section 7 PBAC outcome.

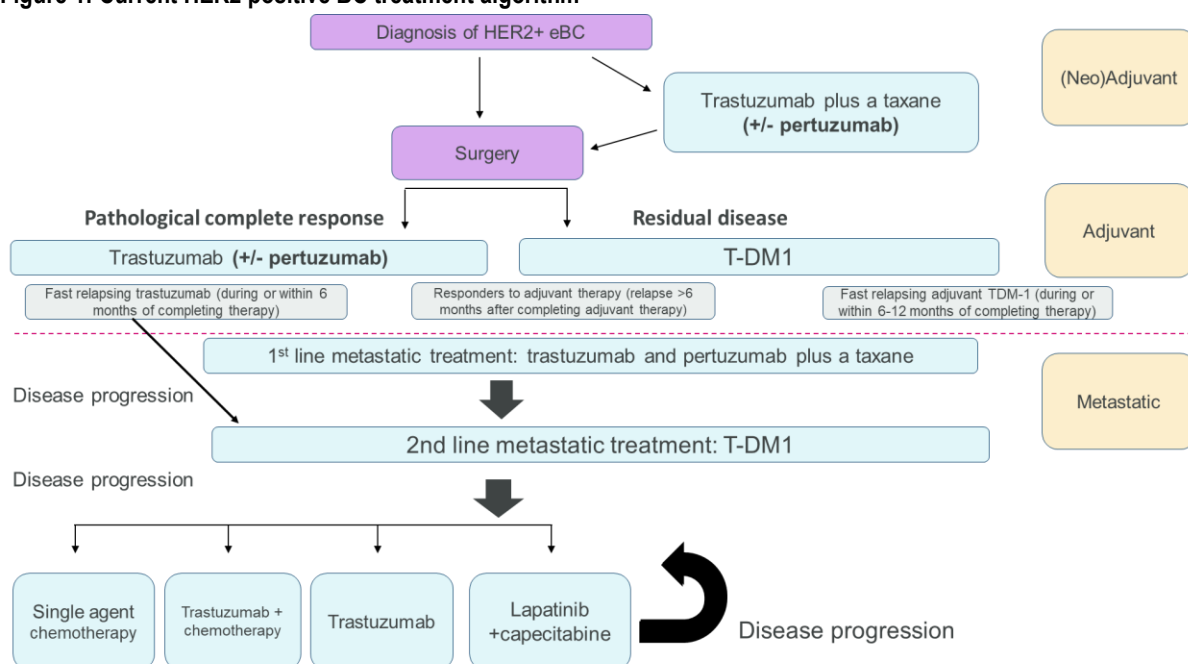
4 Population and disease

- 4.1 Breast cancer is the most common cancer in Australia. Approximately 20% of patients with breast cancer have HER2 positive disease. HER2 positive breast cancer is associated with a higher rate of disease recurrence and mortality than HER2 negative disease¹. The most common first-line treatment used for patients with HER2 positive mBC is pertuzumab and trastuzumab plus a taxane (PTT). The median progression free survival (mPFS) on this treatment combination has been reported as 18.7 months². The treatment currently recommended for patients who have recurrence after first-line HER2-directed treatment for mBC is T-DM1 (Figure 1).
- 4.2 T-DXd is proposed for use as a second-line treatment for mBC (after PTT), or as a first-line treatment for mBC after patients have had a relapse during or within 6 months of adjuvant HER2 directed treatment (either trastuzumab ± pertuzumab, or T-DM1) (Figure 2). The submission did not provide an estimate of the numbers of patients that would be eligible for T-DXd following different prior therapies.

¹ Patel, A, Unni, N & Peng, Y 2020, 'The Changing Paradigm for the Treatment of HER2-Positive Breast Cancer', *Cancers (Basel)*, vol. 12, no. 8, Jul 28.

² Swain, SM, Baselga, J, Kim, SB, Ro, J, Semiglazov, V, Campone, M, Ciruelos, E, Ferrero, JM, Schneeweiss, A, Heeson, S, Clark, E, Ross, G, Benyunes, MC, Cortes, J & Group, CS 2015, 'Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer', *N Engl J Med*, vol. 372, no. 8, Feb 19, pp. 724-734.

Figure 1: Current HER2 positive BC treatment algorithm

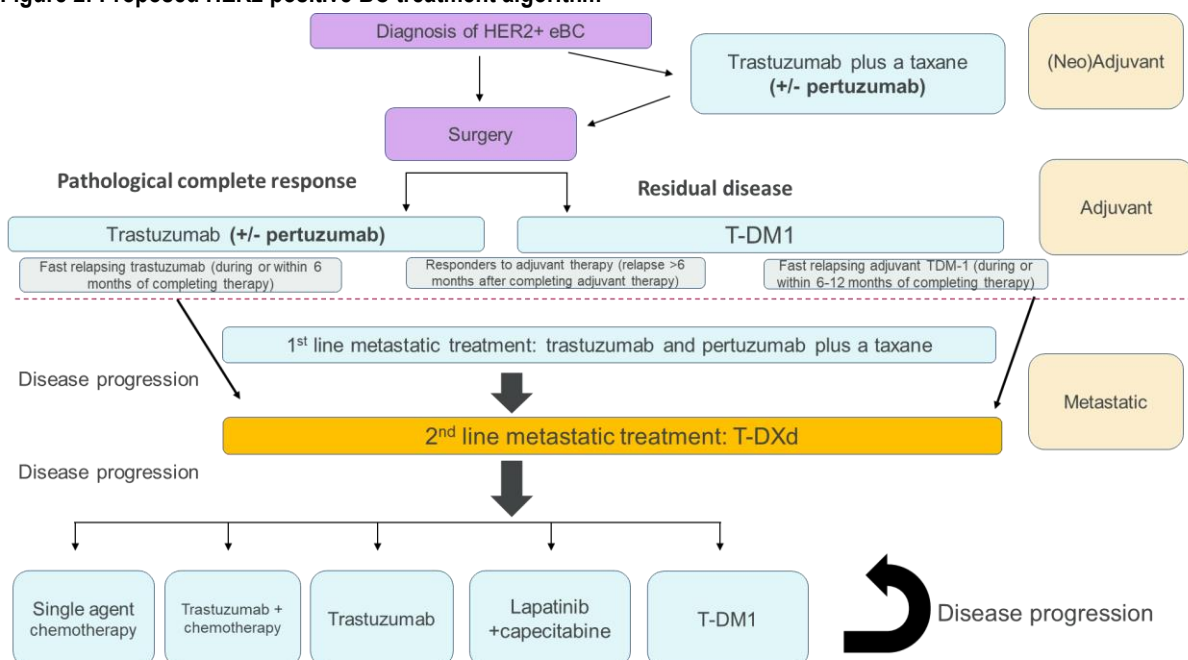


Source: Figure 1.3, p18 of the submission

a: Neoadjuvant therapy may be appropriate for locally advanced breast cancers as well as some larger operable breast cancers to down-stage tumours, either to make them operable or to allow breast-conserving therapy; a: neoadjuvant pertuzumab is currently available via the Roche patient access program.

eBC = early breast cancer; HER2= human epidermal growth factor receptor 2; pCR=pathological complete response; T-DM1 = trastuzumab emtansine.

Figure 2: Proposed HER2 positive BC treatment algorithm



Source: Figure 1.4, p19 of the submission

a: Neoadjuvant therapy may be appropriate for locally advanced breast cancers as well as some larger operable breast cancers to down-stage tumours, either to make them operable or to allow breast-conserving therapy; a: neoadjuvant pertuzumab is currently available via the Roche patient access program.

Note: The PSCR (p2) and the ESC noted that the algorithm should be amended from 'fast relapsing adjuvant T-DM1 (during or within 6-12 months of completing therapy)' to 'fast relapsing adjuvant T-DM1 (during or within 6 months of completing therapy)', to be consistent with the wording of the proposed restriction for T-DXd.

eBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; pCR = pathological complete response; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

- 4.3 The submission described interviews with patients with HER2 positive mBC, conducted by a consumer research and patient advocacy organisation, reporting that disease progression has a significant impact on quality of life. Given patients with HER2 positive disease are younger on average than patients with other types of mBC, they often have dependent family members and therefore have carer-related concerns whilst managing their advanced disease.
- 4.4 T-DXd is an antibody-drug conjugate, with a monoclonal antibody (with the same amino acid sequence as trastuzumab), covalently linked to a topoisomerase 1 inhibitor payload (DXd, a novel exatecan derivative) via a tetrapeptide tumour-selective cleavable linker.

5 Comparator

- 5.1 The nominated comparator was T-DM1, as it is the treatment most likely to be displaced by T-DXd (T-DM1 was used in 69% of HER2 positive mBC patients as second line treatment, based on data between 2015 and 2019 from the Treatment of Advanced Breast Cancer in the HER2 Positive Australian Patient [TABITHA] registry). T-DM1 is the appropriate comparator for the majority of patients.
- 5.2 The evaluation and the ESC considered that for those patients who have residual disease after neoadjuvant treatment and surgery and receive T-DM1 as an adjuvant treatment, and have a relapse during or within 6 months, the appropriate comparator would be standard first-line metastatic treatment (PTT). This is because patients who received T-DM1 in the adjuvant setting and relapse while on treatment or within 6 months are unlikely to receive another line of T-DM1 in the metastatic setting. This comparison (T-DXd vs PTT) was not captured in the DB03 trial and wasn't considered in the economic analysis and financial estimates. The size of this patient group was not estimated in the submission, although the PSCR noted that this group represents a small proportion of adjuvant treated patients (~5%) and that a future RCT is unlikely due to its small size. The PBAC considered that including this patient population for treatment with T-DXd was reasonable based on the current submission (paragraph 3.5).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (4), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website.
- 6.3 The PBAC noted that the advice received from the Breast Cancer Network Australia (BCNA) supported the PBS listing of T-DXd for the treatment of HER2 positive mBC. The BCNA noted that the use of T-DXd was associated with increased PFS, as shown in the DESTINY Breast 03 (DB03) clinical trial, and considered this to be a clinically meaningful benefit for patients with metastatic disease. The BCNA emphasised the clinical benefit observed for patients with brain metastases, and noted that for this subgroup, T-DXd patients were over three times more likely to have a complete or partial response compared with patients receiving T-DM1. The BCNA noted that T-DXd was associated with adverse side effects, including interstitial lung disease and pneumonitis, however considered these to be manageable. The BCNA highlighted the psycho-social role of treatments that reduce the fear associated with cancer recurrence and death. The BCNA also highlighted that the private cost of T-DXd remains high and this cost is currently a significant barrier to treatment for many patients.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the T-DXd submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the DB03 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for T-DXd, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on a comparison with T-DM1.³
- 6.5 The PBAC noted comments from healthcare professionals supporting the PBS listing of T-DXd. It was highlighted that despite the availability of T-DM1, further treatment options were needed for patients with HER2 positive metastatic breast cancer. It was noted that a number of patients do not have access to T-DXd through clinical trials and have limited treatment options in the metastatic setting. The PBAC noted comments were also received from individuals and family members wanting access to T-DXd, highlighting their significant fear of recurrence and early death.

³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Clinical trials

6.6 The submission was based on one head-to-head clinical trial comparing T-DXd to T-DM1 (n=524), DB03.

6.7 Details of the DB03 trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
DB03	Clinical Study Protocol. A Phase III, multicentre, randomized, open label, active-controlled study of trastuzumab deruxtecan (DS-8201A), an anti HER2-antibody drug conjugate versus adotrastuzumab emtansine (T-DM1) for HER2 positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and a taxane.	DS8201-A-U302, Version 5, 23 April 2020
	A Phase 3, Multicentre, Randomized, Open-label, Active controlled. Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2-antibody Drug Conjugate, versus Trastuzumab Emtansine (T-DM1) for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with Trastuzumab and Taxane (DESTINY-Breast 03)	DS8201-A-U302, Version 1, 4 November 2021
	J. Cortés, S-B. Kim, W-P. Chung, S-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L-M. Tseng, V. Petry, C-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, S.A. Hurvitz. LBA1 Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (Pts) with HER2+ metastatic breast cancer (mBC): Results of the randomized phase III DESTINY-Breast03 study.	Annals of Oncology 2021; 32 (5): S1287-S1288
	Hurvitz S, Kim S-B, Chung W-P, Im S-A, Park YH, Hegg R, Kim M-H, Tseng L-M, Petry V, Chung C-F, Iwata H, Hamilton E, Curigliano G, Xu B, Lee C, Liu Y, Cathcart J, Bako E, Verma S, Cortés J. Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast 03.	SABCS symposium presentation December 2021.

Source: Table 2.2, p38 of the submission.

DB03 = DESTINY-Breast 03; SABCS = San Antonio Breast Cancer Symposium

6.8 The key features of the direct randomised trial are summarised in Table 3. The DB03 trial had an overall low risk of bias, although no attempt was made to blind participants to treatment allocation, and the patient-reported outcomes were only collected in participants who were on therapy (not after discontinuation).

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
T-DXd versus T-DM1						
DB03	524	R, OL, MC Ongoing Median follow-up 15.5 months for T-DXd arm, 13.9 months for T-DM1 arm	Low except for HRQoL ^a	HER2+ mBC, progressed after at least one HER2-directed therapy	Primary: PFS Secondary: OS, ORR	PFS, OS, HR-QoL, safety and tolerability

Source: Table 2.3, p41-42 of the submission.

HER2+ = human epidermal growth factor receptor-2; HRQoL = health related quality of life; mBC = metastatic breast cancer; MC = multi-centre; OL = open label; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; R = randomised; T-DM1 =trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

^aParticipants who discontinued treatment were not included in patient-reported outcomes. They were followed up for survival either through direct contact or by collecting public records (e.g. death certificates) as allowed by local laws.

Comparative effectiveness

- 6.9 A 72% reduction in the hazard of progression or death was observed in patients receiving T-DXd compared to those receiving T-DM1, after a median duration of PFS follow-up of 15.5 months in the T-DXd arm and 13.9 months in the T-DM1 arm (Table 4 and Figure 3).
- 6.10 Overall survival (OS) data were considered immature (median time to death was not reached in either treatment arm). In the T-DXd arm, 12.6% of patients had died, and in the T-DM1 arm, 20.2% of patients had died. However, preliminary data showed those in the T-DXd arm had a 45% reduction in the hazard of death compared to those in the T-DM1 arm (Table 4 and Figure 4), with an absolute difference in estimated survival of 8% at 12 months (94.1% vs 85.9%). The Kaplan-Meier (KM) plot shows a slight decrease in the separation between treatment groups after 12 months, suggesting there may be a time-diminishing benefit from T-DXd compared with T-DM1. The PSCR stated that more time will be required to reach median OS in the T-DXd arm compared with previously considered treatments for HER2 positive breast cancer due to the substantial progression-free survival (PFS) benefit provided by T-DXd. The ESC noted that median OS was not reached in both the T-DXd and the T-DM1 arms, and that median OS was reported for the T-DM1 arm (versus lapatinib + capecitabine) in the EMILIA trial as 30.9 months (paragraph 6.8, trastuzumab emtansine PSD, March 2014 PBAC meeting).
- 6.11 The PSCR stated that the second OS interim analysis for the DB03 trial is planned after 153 deaths have occurred and is anticipated in |||||

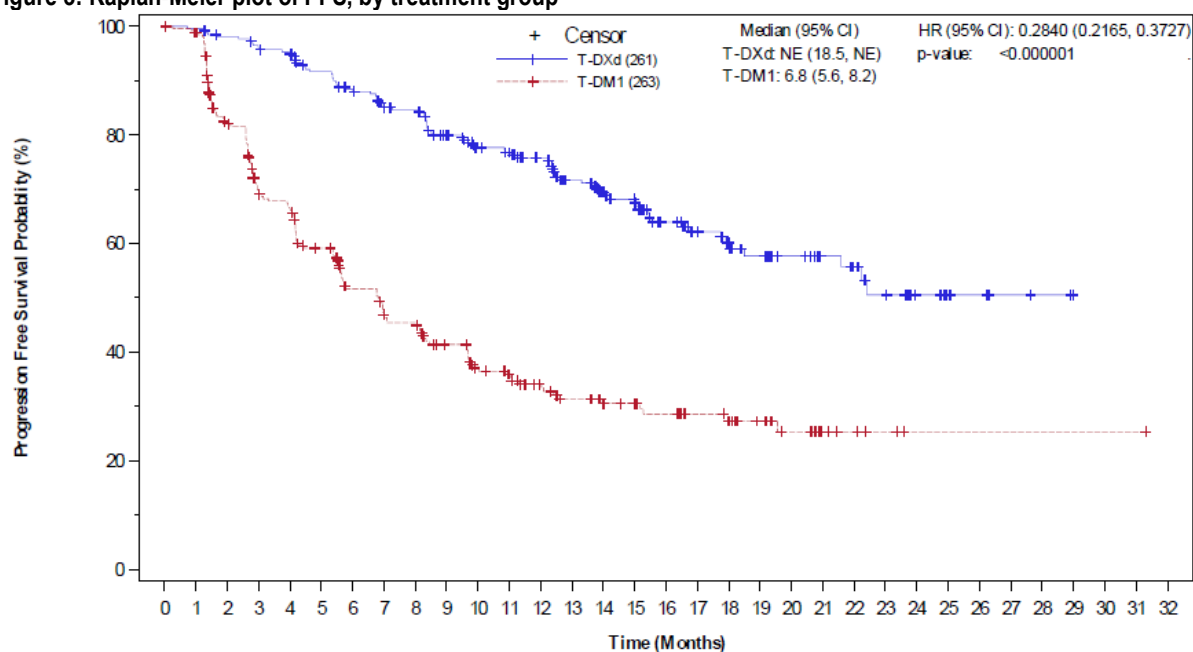
Table 4: Summary of primary efficacy and key secondary efficacy outcomes in DB03 (ITT)

	T-DXd	T-DM1	Absolute difference	HR (95% CI) or p-value
Progression-free survival (full set analysis)				
Progressed, n (%)	87/261 (33.3%)	158/263 (60.1%)	-	0.28 (0.22, 0.37)
Median PFS, months (95% CI)	NR	6.8 (5.6, 8.2)	NE	-
% not progressed at 12 months (95% CI)	75.8 (69.8, 80.7)	34.1 (27.7, 40.5)	41.6 (33.9, 49.4)	-
% not progressed at 24 months (95% CI)	50.5 (39.9, 60.2)	25.3 (18.4, 32.9)	25.2 (17.1, 33.1)	-
Overall survival (full set analysis)				
Deaths, n (%)	33/261 (12.6%)	53/263 (20.2%)	-	0.55 (0.36, 0.86)
Median months OS (95% CI)	NR	NR	NE	-
% alive at 12 months (95% CI)	94.1 (90.3, 96.4)	85.9 (80.9, 89.7)	8.3 (3.3, 13.4)	-
% alive at 24 months (95% CI)	80.8 (73.0, 86.6)	73.7 (66.1, 79.9)	7.1 (-0.1, 14.2)	-
Overall response rate				
ORR, n/N (%)	208/261 (79.7%)	90/263 (34.2%)	45.5%	p<0.0001
(95% CI)	(74.3, 84.4)	(28.5, 40.3)	(37.6, 53.4)	-
CR, n (%)	44 (16.1%)	23 (8.7%)	7.4%	-
PR, n (%)	166 (63.6%)	67 (25.5%)	38.1%	-
SD, n (%)	44 (16.9%)	112 (42.6%)	-25.7%	-
PD, n (%)	3 (1.1%)	15 (5.7%)	-4.6%	-

Source: Table 2.11, p60 of the submission, Table 2.12, p63 of the submission, and Table 2.13, p68 of the submission. Absolute differences calculated during evaluation. Statistically significant results in **bold**.

CI = confidence interval; CR = complete response; HR = hazard ratio; ITT = intention to treat; n = number of participants with event; N = total participants in group; NE = not estimable; NR = not reached; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

Figure 3: Kaplan-Meier plot of PFS, by treatment group



Subjects still at Risk:

T-DXd (261) 261 256 250 244 240 224 214 202 200 183 168 164 150 132 112 105 79 64 53 45 36 29 25 19 10 6 5 3 2 0

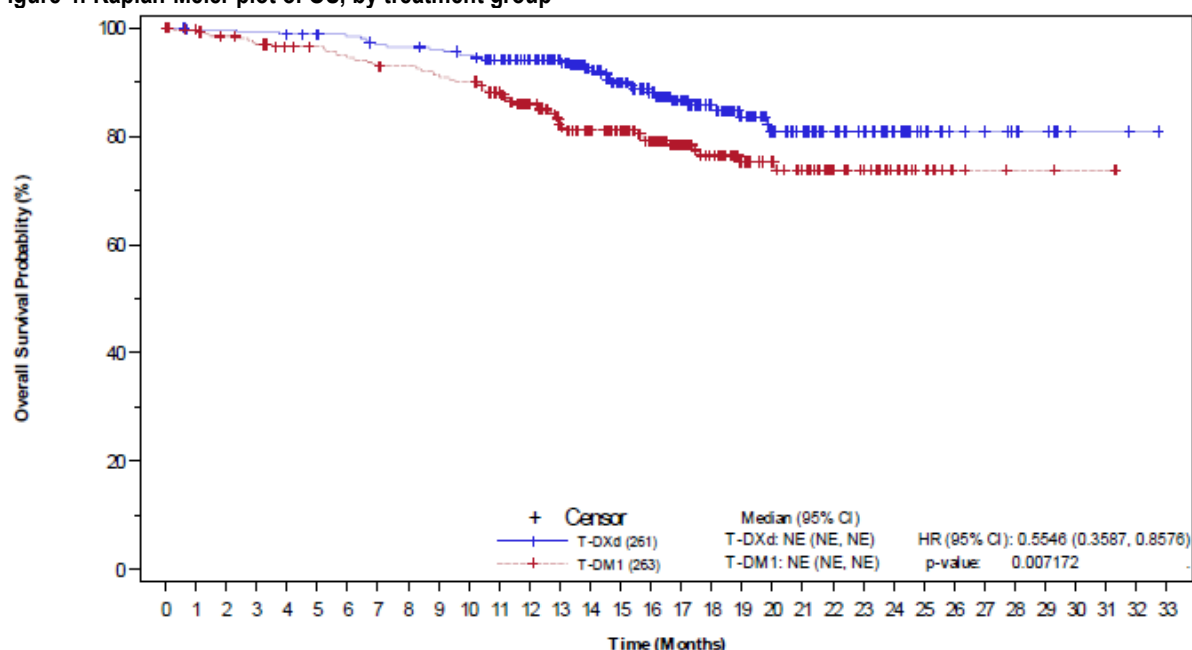
T-DM1 (263) 263 252 200 163 155 132 108 96 93 78 65 60 51 43 37 34 29 23 21 16 12 8 6 4 1 1 1 1 1 1 1 0

Source: Figure 8.1, p84, DB03 CSR, Attachment 8 of the submission

CI = confidence interval; HR = hazard ratio; NE = not estimable; PFS = progression free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan

Data cut-off 21 May 2021

Figure 4: Kaplan-Meier plot of OS, by treatment group



Subjects still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Source: Figure 8.4, p96, DB03 CSR, Attachment 8 of the submission

CI = confidence interval; HR = hazard ratio; NE = not estimable; OS = overall survival; T-DXd = trastuzumab deruxtecan

Data cut-off 21 May 2021

- 6.12 The impact of treatment on patients' health status was assessed using the EuroQol 5D 5-level version (EQ-5D-5L) at baseline and at treatment discontinuation. Treatment was discontinued upon progression or unacceptable toxicity. This approach would therefore be likely to introduce selection bias. No minimum clinically important difference (MCID) for EQ-5D-5L was stated in the submission. The mean change in scores between baseline and treatment endpoint were small in both arms (-0.01 and -0.02 for T-DXd and T-DM1, respectively). These changes are smaller than MCIDs published for EQ-5D-5L in the literature, which range from 0.072 to 0.101⁴.
- 6.13 Single arm evidence from the DB01 trial was provided in an Appendix to the submission for the proposed subpopulation excluded from the DB03 trial (those who received T-DM1 as an adjuvant therapy and progressed either during treatment or within 6 months therapy). These 'rapid relapsers' received T-DXd and had a median PFS of 19.4 months (95%CI 14.1, 25.0), and median OS of 29.1 months (95%CI 24.6, 36.1). The PSCR added that the mature PFS and OS data from the DB01 trial, in a

⁴ Henry, EB, Barry, LE, Hobbins, AP, McClure, NS & O'Neill, C 2020, 'Estimation of an Instrument-Defined Minimally Important Difference in EQ-5D-5L Index Scores Based on Scoring Algorithms Derived Using the EQ-VT Version 2 Valuation Protocols', *Value Health*, vol. 23, no. 7, Jul, pp. 936-944.

significantly more heavily pre-treated population than in the DB03 trial, provides reassurance that the results observed to date in the DB03 trial will translate to a statistically and clinically significant extension to OS for patients treated with T-DXd. Notwithstanding, the ESC noted that the comparative effectiveness of T-DXd versus PTT, in a population who have progressed while on or within 6 months of having adjuvant T-DM1, is unknown.

Comparative harms

6.14 Table 5 presents a summary of adverse events, based on the DB03 trial. The rate of serious treatment-related adverse events was similar between treatment arms (19.1% for T-DXd vs 18.0% for T-DM1).

Table 5: Summary of key adverse events in the DB03 trial (safety analysis set)

Outcome	T-DXd (median 14.3 months) n with event/257 (%)	T-DM1 (median 6.9 months) n with event/261 (%)	RR (95% CI)
Any TEAE	256 (99.6)	249 (95.4)	1.04 (1.02, 1.07)
TEAE with CTCAE Grade $\geq$ 3	134 (52.1)	126 (48.3)	1.08 (0.91, 1.28)
Serious TEAE	49 (19.1)	47 (18.0)	1.06 (0.74, 1.52)
TEAE associated with study drug discontinuation	35 (13.6)	19 (7.3)	1.87 (1.10, 3.18)
TEAE associated with study drug interruption	113 (44.0)	61 (23.4)	1.88 (1.45, 2.44)
TEAE associated with dose reduction	55 (21.4)	33 (12.6)	1.69 (1.14, 2.51)
TEAE associated with an outcome of death	5 (1.9)	5 (1.9)	1.02 (0.30, 3.47)
Grade $\geq$ 3 neutropenia	49 (19.1)	8 (3.1)	6.22 (3.01, 12.97)
Grade $\geq$ 3 anaemia	19 (7.4)	15 (5.7)	1.29 (0.67, 2.48)
Grade $\geq$ 3 thrombocytopenia	19 (7.4)	67 (25.7)	0.29 (0.18, 0.47)
Grade $\geq$ 3 leukopenia	17 (6.6)	1 (0.4)	17.26 (2.31, 128.78)
Grade $\geq$ 3 nausea	17 (6.6)	1 (0.4)	17.26 (2.31, 128.78)
Grade $\geq$ 3 fatigue	15 (5.8)	2 (0.8)	7.62 (1.76, 32.97)
Serious interstitial lung disease	6 (2.3)	1 (0.4)	6.09 (0.74, 50.26)
Interstitial lung disease (any grade) ^a	27 (10.5)	5 (1.9)	5.48 (2.14, 14.02)

Source: Table 2.23, pp81-82 of the submission and Table 2.24, pp82-83 of the submission. RR calculated during the evaluation; **bold** denotes a statistically significant difference.

CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; n = number of participants reporting data; RR = relative risk; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE: treatment-emergent adverse event

If a participant reported 1 or more TEAEs, that subject was counted only once in each relevant cell.

^aInterstitial lung disease (ILD) cases which were adjudicated as being drug-related. 2 cases in the T-DXd arm were grade 3, the remainder grade 1 – 2.

Benefits/harms

6.15 A summary of the comparative benefits and harms for T-DXd versus T-DM1 is presented in Table 6.

Table 6: Summary of comparative benefits and harms for T-DXd vs T-DM1

	T-DXd	T-DM1	Absolute difference	HR (95% CI) or p-value		
Progression-free survival (full set analysis)						
Progressed, n (%)	87/261 (33.3%)	158/263 (60.1%)	-	0.28 (0.22, 0.37)		
Median PFS, months (95% CI)	NR	6.8 (5.6, 8.2)	NE	-		
% not progressed at 12 months (95% CI)	75.8 (69.8, 80.7)	34.1 (27.7, 40.5)	41.6 (33.9, 49.4)	-		
% not progressed at 24 months (95% CI)	50.5 (39.9, 60.2)	25.3 (18.4, 32.9)	25.2 (17.1, 33.1)	-		
Overall survival (full set analysis)						
Deaths, n (%)	33/261 (12.6%)	53/263 (20.2%)	-	0.55 (0.36, 0.86)		
Median months OS (95% CI)	NR	NR	NE	-		
% alive at 12 months (95% CI)	94.1 (90.3, 96.4)	85.9 (80.9, 89.7)	8.3 (3.3, 13.4)	-		
% alive at 24 months (95% CI)	80.8 (73.0, 86.6)	73.7 (66.1, 79.9)	7.1 (-0.1, 14.2)	-		
Overall response rate						
ORR n/N (%)	208/261 (79.7%)	90/263 (34.2%)	45.5%	p<0.0001		
(95%CI)	(74.3, 84.4)	(28.5, 40.3)	(37.6, 53.4)	-		
CR n (%)	44 (16.1%)	23 (8.7%)	7.4%	-		
PR n (%)	166 (63.6%)	67 (25.5%)	38.1%	-		
SD n (%)	44 (16.9%)	112 (42.6%)	-25.7%	-		
Harms						
	T-DXd n/N	T-DM1 n/N	RR (95% CI)	Event rate/100 patients		RD
				T-DXd	T-DM1	
TEAE with CTCAE Grade ≥ 3	134/257	126/261	1.08 (0.91, 1.28)	52.1	48.3	3.8
Serious TEAE	49/257	47/261	1.06 (0.74, 1.52)	19.1	18.0	1.1
TEAE associated with study drug interruption	113/257	61/261	1.88 (1.45, 2.44)	44.0	23.4	20.6
Grade ≥3 neutropenia	49	8	6.22 (3.01, 12.97)	19.1	3.1	16.0
Grade ≥3 thrombo-cytopenia	19	67	0.29 (0.18, 0.47)	7.4	25.7	-18.3
Grade ≥3 nausea	17	1	17.26 (2.31, 128.78)	6.6	0.4	6.2
Interstitial lung disease (any grade) ^a	27	5	5.48 (2.14, 14.02)	10.5	1.9	8.6

Source: generated during the evaluation based on Table 2.11, p60, Table 2.12, p63, Table 2.13, p68, Table 2.14, p69, Table 2.23, p81 of the submission.

CI = confidence interval; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; HR = hazard ratio; n = number of participants reporting data; NE = not estimable; ORR = overall response rate; OS = overall survival; PR = partial response; RD = risk difference; RR = relative risk; SD = stable disease; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

If a participant reported 1 or more TEAEs, that subject was counted only once in each relevant cell.

Statistically significant results have been **bolded**.

^aInterstitial lung disease (ILD) cases which were adjudicated as being drug-related. 2 cases in the T-DXd arm were grade 3, the remainder grade 1 – 2.

6.16 On the basis of direct evidence presented by the submission, for every 100 patients treated with T-DXd in comparison with T-DM1 over 24 months:

- Approximately 25 fewer patients would have progressive disease or died.

- Approximately 7 fewer patients would have died.

In addition, for every 100 patients treated with T-DXd in comparison with T-DM1, over a median duration of PFS follow-up of 15.5 months in the T-DXd arm, and 13.9 months in the T-DM1 arm:

- Approximately 4 additional patients would experience a treatment related adverse event with grade ≥ 3 .
- Approximately 16 additional patients would experience grade ≥ 3 neutropenia (low neutrophil count, which are a type of white blood cells). Low white blood cell levels lead to an increase in the risk of infection.
- Approximately 18 fewer patients would experience grade ≥ 3 thrombocytopenia (low blood platelet count).
- Approximately 4 additional patients would experience grade ≥ 3 nausea.
- Approximately 9 additional patients would experience drug-related interstitial lung disease (ILD; scarring of the lungs) (any grade, mostly grade 0–2, no grade 4–5). This is an adverse event of special interest, and patients on T-DXd receive monitoring and discontinuation of treatment if there is any sign of ILD due to strict management for ILD.

Clinical claim

- 6.17 The submission described T-DXd as superior in terms of effectiveness to T-DM1. The PBAC agreed with the evaluation and ESC that despite the immaturity of the OS data, this claim was adequately supported by the large effect of T-DXd on PFS (72% reduction in hazard of progression or death).
- 6.18 The submission described T-DXd as non-inferior in terms of safety to T-DM1 (albeit with a different safety profile). Those in the T-DXd arm were more likely to experience grade ≥ 3 neutropenia than those in the T-DM1 arm (19.1% vs 3.1%), as well as a higher rate of ILD (10.5% vs 1.9%). Conversely, T-DXd was associated with fewer cases of thrombocytopenia than T-DM1 (7.4% vs 25.7%). Despite these differences in safety profile, there was virtually no difference between arms with respect to serious treatment-related adverse events (19.1% vs 18.0% respectively), and therefore the evaluation considered that the claim of non-inferior safety may be reasonable.
- 6.19 In contrast, the ESC considered that the claim of non-inferior safety is not supported. The ESC noted that while similar rates of serious treatment-related adverse events were reported in both arms, T-DXd was associated with adverse events driven by grade ≥ 3 clinical symptoms, which are more likely to have significant impact on patients and are also more likely to be associated with hospital admission compared with the treatment-related adverse events reported with T-DM1 (i.e. thrombocytopenia). As such, the ESC considered that T-DXd has a different, and potentially clinically more significant, toxicity profile compared to T-DM1.

- 6.20 The sponsor maintained in the pre-PBAC response that T-DXd demonstrated similar safety to T-DM1 and provided a reference to an updated safety summary presented at the American Society of Clinical Oncology (ASCO) annual meeting (2022) reporting exposure-adjusted incidence rates (EAIRs) for grade >3 treatment-emergent adverse events (TEAEs) as 0.42 and 0.7 for T-DXd and T-DM1, respectively. It was argued that due to the longer treatment duration associated with T-DXd versus T-DM1, EAIRs were a more accurate reflection of comparative safety than unadjusted rates of events. The sponsor also highlighted that no significant decrement to QoL was observed for subjects in both treatment arms in the DB03 trial. While the PBAC agreed with the ESC that T-DXd has inferior safety compared to T-DM1, it considered the side effects associated with T-DXd to be manageable, noting the importance of quality use of medicines (QUM) activities to educate clinicians and patients on monitoring and management of interstitial lung toxicity.

Economic analysis

- 6.21 The submission presented a stepped economic evaluation based on the direct randomised trial DB03. The type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation are presented in Table 7.

Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	T-DXd vs T-DM1
Time horizon	15 years in the model base-case versus less than two years in the DB03 clinical trial.
Outcomes	Life years and quality adjusted life years.
Methods used to generate results	Partitioned survival model (i.e. area under the curve).
Health states	Progression-free, post-progression and dead.
Cycle length	21 days (matching the treatment cycle length), with half cycle correction.
Allocation to health states and extrapolation method	Health state allocation followed the observed PFS and OS KM data until the median duration of PFS follow-up time of the interim analysis of the DB03 clinical trial (15.5 months for the T-DXd arm and 13.9 months for the T-DM1 arm). After this time point, PFS was extrapolated with independent parametric functions. OS was extrapolated past the median time of PFS follow-up with dependent parametric functions. The evaluation considered that the choice of the observed data truncation based on median follow-up for PFS in each arm was not well justified. Observed time-to-event data are preferred up to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free. In this case, it is likely to be closer to the two year time point. Time on treatment was based on the observed time to treatment discontinuation KM data from the DB03 clinical trial up to 18 months for the T-DXd arm and 7 months for the T-DM1 arm. Time to treatment discontinuation was extrapolated past this time point with independently-fitted parametric functions. The choice of time point for extrapolation of time on treatment did not have a marked impact on the modelled results. 84% of incremental QALYs and 46% of incremental costs occur in the extrapolated period (beyond approximately 20 months of observed trial data).
Health related quality of life	Utilities for the progression free health state were based on treatment specific DB03 trial based EQ-5D questionnaires.

Component	Summary
	Utilities for the post-progression health state were based on an algorithm (Lloyd et al 2006 ⁵).
Costs	The submission estimated costs associated with T-DXd and T-DM1, adverse events from treatment, disease management costs for pre-progression and post-progression health states, subsequent therapy costs and end-of-life costs. Key concerns of the evaluation relate to double counting end-of-life costs (informed by an Australian costing study⁶), post-progression management costs and subsequent therapy costs. The method for estimating subsequent therapies was not well justified and considerably favours the T-DXd arm.

Source: Table 3.1, p102 of the submission.

DB03 = DESTINY Breast 03 trial; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; QALYs = quality adjusted life years; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

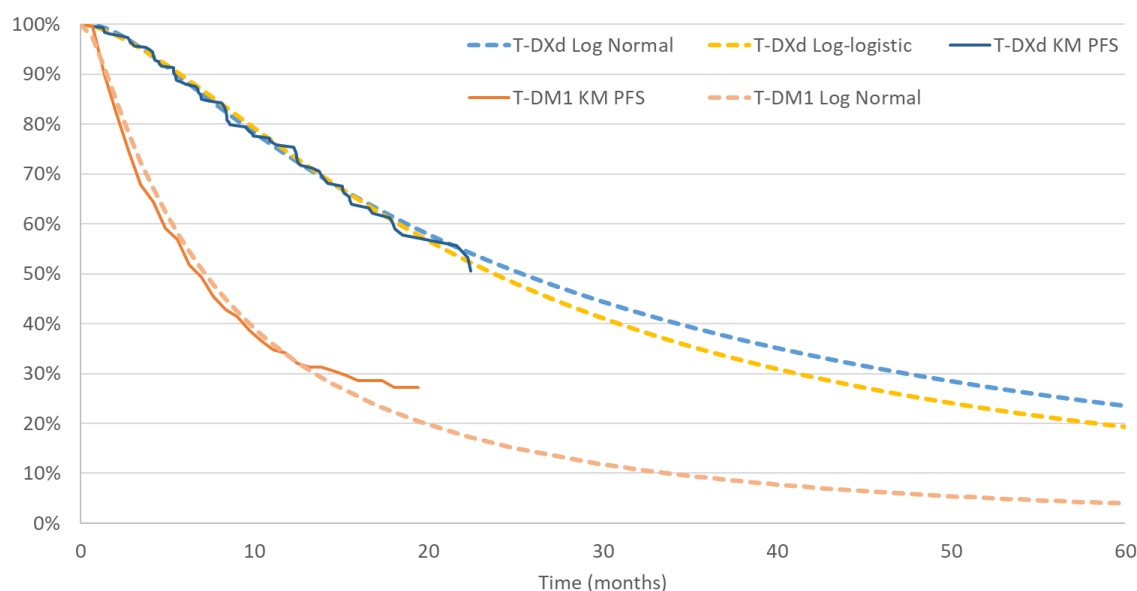
- 6.22 Health state membership for both T-DXd and T-DM1 was determined by observed KM estimates for PFS and OS up to 15.5 months and 13.9 months (median duration of PFS follow-up for T-DXd and T-DM1, respectively). Independent parametric functions were used to extrapolate PFS from the data truncation point to 15 years. Dependent parametric functions were used to extrapolate OS from the data truncation point to 15 years. The PBAC considered that a time horizon of 15 years is appropriate, noting that longer term data from recent studies now suggest 5-year survival rates of 25% and higher.
- 6.23 The point of observed data truncation is based on the median follow-up for PFS for each treatment arm (15.5 months for T-DXd and 13.9 months for T-DM1). It is likely that there are adequate numbers of patients remaining at risk in the KM curves for both PFS and OS to extend the data truncation point closer to 20 months. This is particularly important given that the latter half of the PFS and OS KM curves appear to be less favourable to T-DXd than the initial 10 months. The evaluation applied extrapolation from 18 months in an alternative base case (see multivariate analysis in Table 11 below) for both T-DXd and T-DM1 arms (PFS and OS). The PSCR stated that 18 months is not reasonable as a time point for data truncation for PFS or OS due to the prolonged time between the steps in the KM curves and the extensive censoring from 11 months, respectively. However, the PBAC agreed with the ESC that 18 months is an appropriate time for observed data to be truncated and extrapolation to start as there are a sufficient number of patients remaining at risk (20% of the patient cohort). The ESC and the PBAC noted that early truncation points favoured T-DXd.

⁵ Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90.

⁶ Reeve R, Srasuebku P, Langton JM, Haas M, Viney R, Pearson S-A. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliative Care. 2018;17(1):1-10.

- 6.24 As the proportional hazards assumption does not hold for PFS, the submission used independently fitted parametric functions to extrapolate the PFS curve in the model. The submission used the log-normal parametric function for T-DXd (most favourable). The submission used the log-normal parametric function for T-DM1 (which is less favourable than several other options for T-DM1).
- 6.25 There is no clear difference in the statistical fit (based on AIC and BIC) between the log-normal function and the log-logistic function for T-DXd PFS data. The use of a log-logistic function to extrapolate T-DXd PFS may better reflect the declining treatment effect toward the end of the observed KM data (Figure 5). An alternative approach would be to nominate a parametric function for T-DM1 PFS that results in greater PFS, however the options that were available in the model may not be plausible. The use of a log-logistic parametric function for T-DXd PFS extrapolation resulted in a 9.7% increase in the incremental cost effectiveness ratio (ICER) when applied to the base case. The PSCR stated that there is no meaningful difference in the goodness-of-fit statistics between the log-logistic and log-normal functions and maintained that the log-normal function provides a more clinically plausible estimate of the long term PFS for T-DXd. Notwithstanding, the PBAC agreed with ESC and the evaluation that the log-logistic parametric function for T-DXd PFS better reflected the end of the observed KM data.

Figure 5: Base case parametric functions for the extrapolation of PFS in the model (log normal for both T-DXd and T-DM1), and alternative extrapolation for T-DXd (log logistic)



Source: generated during the evaluation of the submission's economic model.

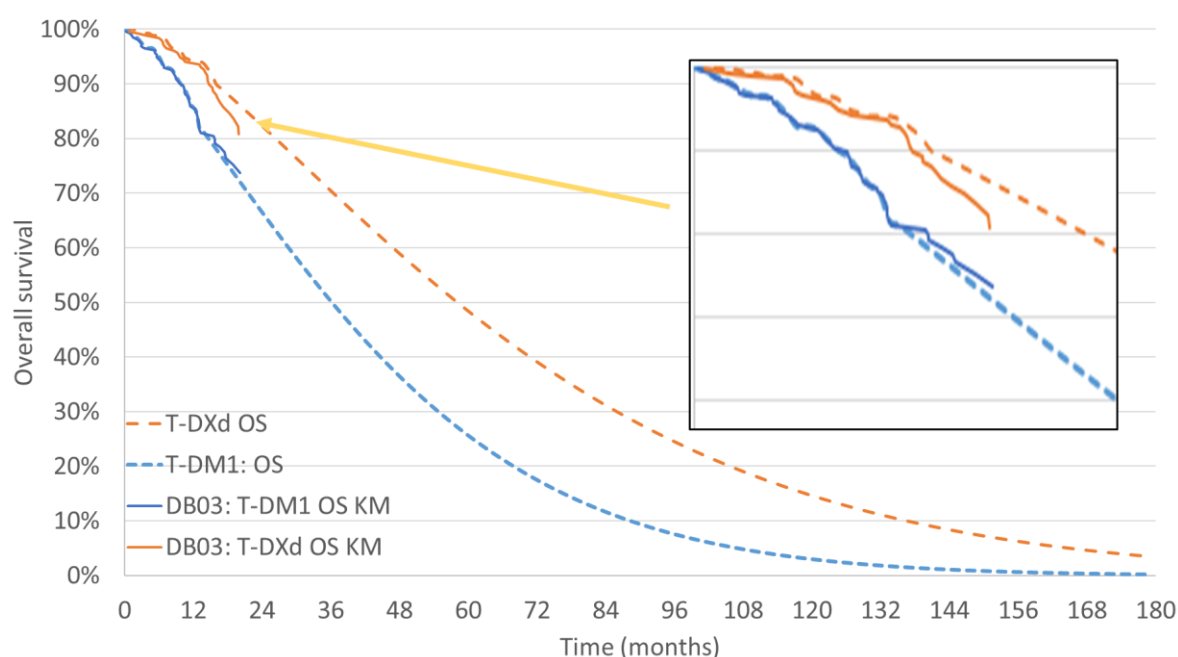
KM = Kaplan-Meier curve; PFS = progression free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The log-normal curve, and log-logistic curve are the two best fitting curves using AIC and BIC for T-DXd progression free survival.

- 6.26 The submission has stated that proportional hazards may hold for OS and has used dependently fitted Weibull parametric functions to extrapolate OS in the model. While initially – to approximately 10 months – the assumption of proportional hazards does

appear reasonable, after this timepoint the smoothed Schoenfeld residuals plot bends upward, indicating the difference in risk of death (treatment effect) is reducing hereafter (Figure 6). Although affected by a reduction of patients at risk, the Schoenfeld residuals appear to indicate no treatment effect from approximately 16 months onward. Given that the model extrapolates OS and PFS from approximately 15 months to 15 years, the assumption of ongoing proportional hazards is not likely to be reasonable and greater consideration to the shape of the latter half of the KM curve may be appropriate.

Figure 6: Dependent Weibull extrapolation for overall survival for T-DXd and T-DM1, with DB03 KM curve data



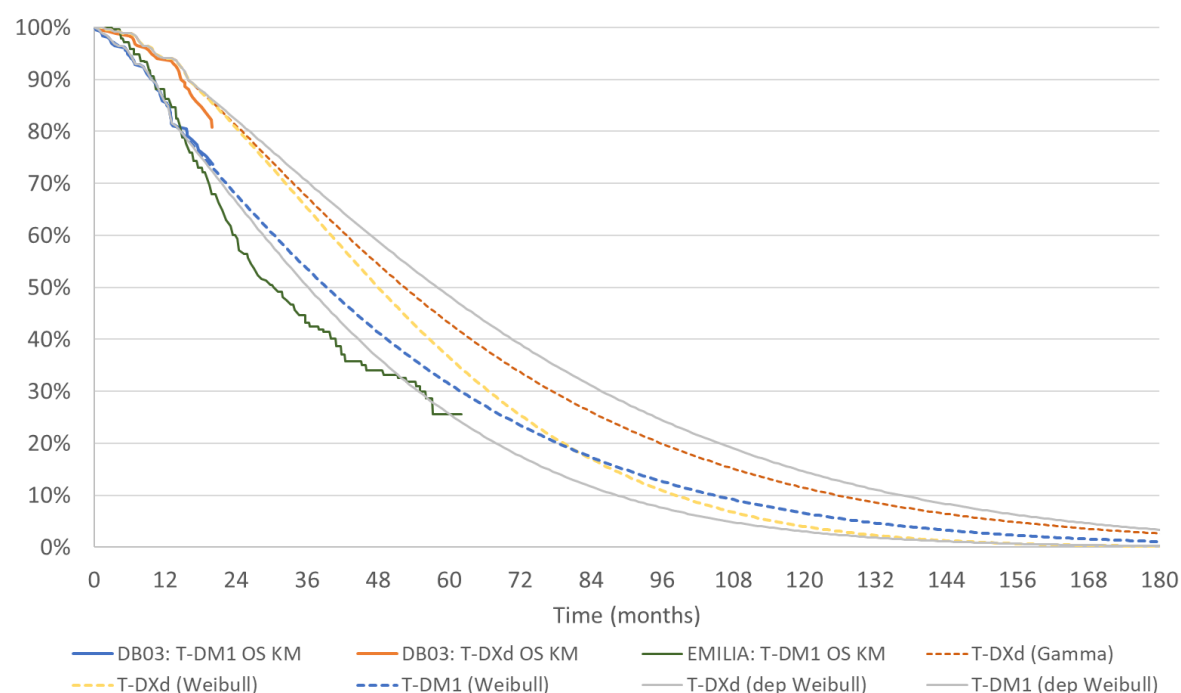
Source: generated during the evaluation from the economic evaluation spreadsheet.

DB03 = DESTINY Breast 03; KM = Kaplan-Meier curve; OS = overall survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

- 6.27 The dependent Weibull extrapolation for OS in the model predicts a divergence of the curves until approximately 7 years (see Figure 6). The observed data in the KM curves, however, appear to be reasonably parallel from approximately 13 months. Using independently fitted parametric functions that may better reflect the latter half of the KM curves results in an increase in the ICER of between 14% and 27%.
- 6.28 An alternative base case was presented by the evaluation with independently fit parametric functions for OS (Figure 7). The Weibull function was used to extrapolate T-DM1 OS. This extrapolation was compared against the OS survival in a randomised trial of T-DM1 vs lapatinib plus capecitabine (EMILIA). The Weibull function that was fit for T-DM1 predicted similar, or slightly higher survival than T-DM1 observed at 5 years in the EMILIA trial, and appears to be a reasonable parametric function for predicting long term survival. The best statistical fitting curve was the log-logistic, however this predicted implausibly high survival.

- 6.29 The choice of an appropriate function for extrapolating OS for the T-DXd arm in the alternative base case has been based on statistical fit and plausibility of long-term survival. Statistically, the best fitting curve for OS for T-DXd was the log-logistic curve, however this was excluded due to the prediction a substantial number of people remaining alive at 15 years. The next best fitting curves were gamma and Weibull. The Weibull curve crossed the extrapolated T-DM1 curve, which may be plausible based on the changing shape of the KM curves (paragraph 6.10), however may not be consistent with the observed benefits in PFS. Therefore, the PBAC noted that the evaluation selected the independently fit gamma function for the T-DXd curve. This selection (combined with an independently fit Weibull curve for T-DM1) results in an increase in the ICER of approximately 14.3%.

Figure 7: Independently fitted overall survival parametric functions for T-DXd and T-DM1, with KM estimates for DB03 and the T-DM1 arm of EMILIA



Source: generated during the evaluation from the economic evaluation spreadsheet.

DB03 = DESTINY Breast 03; KM = Kaplan-Meier curve; OS = overall survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The base case has used the dependent (dep) Weibull function. An alternative base case is presented in the commentary using the independent Weibull for T-DM1 and the independent Gamma for T-DXd.

- 6.30 The PSCR stated that the use of a dependently fit Weibull function for OS extrapolation is supported by the fact that the proportional hazards assumption held during a period which had the greatest certainty (sufficient patient numbers and little censoring). Notwithstanding, the ESC considered that maintaining a treatment effect on OS for the length of the nominated time horizon (15 years) with a dependently fit function was not reasonable given the uncertainty associated with the OS data from month 10. It considered it was not reasonable to assess the proportional hazards assumption

based on only the early section of the overall survival curve. Therefore, the ESC agreed with the evaluation that independently fit parametric functions for OS extrapolation were more appropriate and considered that the OS data suggests a diminishing treatment effect (curve convergence) should also be considered.

- 6.31 The choice of parametric function for the extrapolation of time on treatment curves for T-DM1 does not meaningfully affect the ICER as the time on treatment curve is relatively mature. The submission has nominated the generalised gamma parametric function for extrapolating time on treatment for the T-DXd curve. Extrapolation using this method does not account for the relationship between time on treatment and the pre-progression health state. Using the submission's approach, the proportion of people who remain progression-free that are receiving treatment consistently declines. It is unclear whether this is a reasonable assumption given that those that cease treatment are likely to be at a greater risk of progression.
- 6.32 The submission applied utility estimates derived from the DB03 trial for the pre-progression health state. For the post-progression health state, the small reduction in quality of life observed in the DB03 trial is not likely to reflect the average utility of the whole health state, and therefore the submission has used published utility values. While the ICER is sensitive to the choice of utilities, this approach is likely reasonable.
- 6.33 Disutilities have been applied to the proportion of patients experiencing Grade ≥ 3 TEAEs. The submission has used generalised estimating equations (GEE) to derive the utilities based on EQ-5D data from the DB03 trial. This method is difficult to validate. The inclusion of TEAE related disutilities, which are entirely applied in the first cycle of the model, has almost no impact on the ICER.
- 6.34 The model has incorporated costs associated with the use of medicines, disease management (different for each health state), subsequent anti-cancer therapies, end-of-life and TEAEs (Table 8). The economic model does not appear to be sensitive to the cost inputs of the model, apart from those related to treatment (T-DXd, T-DM1 and subsequent anti-cancer therapies).

Table 8: Incremental costs (discounted) disaggregated across resource type

Resource item	T-DXd (\$)	T-DM1 (\$)	Incremental (\$)	% of incremental
Medicines ^a				121%
Disease management				3%
Subsequent anticancer therapies				-21%
End-of-life				-3%
TEAEs				-0.01%
Total costs				100%

^a Including administration costs

Source: generated during the evaluation from the "Results" worksheet of the economic evaluation spreadsheet.

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAEs = Treatment emergent adverse events.

- 6.35 The cost of post progression disease management and subsequent anti-cancer therapies are applied in each cycle to the proportion of individuals remaining in the post progression health state until death or the end of the model time horizon. End-

of-life costs were derived from an Australian study⁷ that recorded costs associated with disease management and medicines; the concurrent application of these costs with costs associated with post progression disease management and subsequent anti-cancer therapies likely represents double counting. An alternative base case was presented by the evaluation that removes 6 months of subsequent anti-cancer therapy costs (Table 11), and 6 months of disease management costs from the end-of-life costs. The approach taken to estimate the cost of end-of-life care in the evaluation was accepted in the PSCR and the Sponsor agreed to revise the six-month cost in Reeve et al (2018) from \$49,977 to \$27,107.

- 6.36 The impact of subsequent anti-cancer therapies on the ICER was substantial and represented a marked cost-offset for the T-DXd arm. However, the method for estimating costs associated with subsequent anti-cancer therapies was flawed. The base case assumed that 29.9% and 62.4% of patients who received T-DXd and T-DM1, respectively, received subsequent anti-cancer therapies. This estimate reflects the number of people who have received subsequent therapies in each arm of DB03. However, this does not account for the differences in progression events across the arms. Of those who have progressed, approximately 100% of patients in each arm receive subsequent anti-cancer therapies. Therefore, the cost of subsequent anti-cancer therapies should be applied to the proportion of patients in the post-progression health state in the model and not to a reduced fraction of these patients. This was corrected in an alternative base case (Table 11) and had a substantial impact on the ICER. The pre-PBAC response acknowledged that the estimates were based on observed data from the DB03 trial and that over the time horizon of the model it is possible that a higher proportion of patients in both arms could receive subsequent anti-cancer therapies following disease progression.
- 6.37 The submission estimated the cost of subsequent anti-cancer therapies by multiplying the unit cost (per model cycle) of a particular subsequent therapy by the likelihood that it would be used at any time by patients who received subsequent therapies in DB03 and applied this to every cycle in the post-progression health state. The cost is modified by the proportion of patients who are modelled to receive subsequent therapies (i.e., 29.9% in the T-DXd arm and 62.4% in the T-DM1 arm). The evaluation considered this approach to be flawed. Subsequent therapies observed in DB03 represent multiple lines of subsequent therapies that are not used concurrently. Costing all the subsequent therapies using the approach in the model results in all subsequent lines of therapy being applied in each cycle. Adding up the percentages of patients (who receive subsequent therapies) that receive a particular subsequent therapy regimen (Table 9), results in 197% and 237% of patients who receive

⁷ Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson S-A. Health care use and costs at the end-of-life: a comparison of elderly Australian decedents with and without a cancer history. *BMC Palliative Care*. 2018;17(1):1-10.

subsequent therapies being assigned to a particular regimen. For example, in the T-DM1 arm, 88% of patients receiving subsequent therapies are costed, each cycle, to receive lapatinib + capecitabine, and an additional 77% of patients in the same arm are costed to receive capecitabine alone. Patients receiving capecitabine alone cannot occur at the same time as receiving combination lapatinib + capecitabine, and this example highlights the approach of costing these in each cycle is inappropriate.

Table 9: Subsequent treatments used in the economic model

	T-DXd			T-DM1		
	n	%	Alternative base case %	n	%	Alternative base case %
Patients receiving subsequent Rx	N = 1	-		N = 1	-	
Trastuzumab SC	1	29%	15%	1	40%	17%
T-DXd	1	0%	0%	1	0%	0%
T-DM1	1	55%	28%	1	0%	0%
Paclitaxel	1	6%	3%	1	10%	4%
Paclitaxel + trastuzumab SC	1	4%	2%	1	9%	4%
Lapatinib + capecitabine	1	35%	18%	1	88%	37%
Tamoxifen	1	17%	8%	1	13%	5%
Capecitabine	1	51%	26%	1	77%	32%
Total	1	197%	100%	1	237%	100%

Source: Table 3.18, p139 of the submission

Note: the subsequent anti-cancer treatments reported in DB03 is presented in Table 3.17, p138 of the submission. The anticancer treatments reported in DB03 differ slightly from those applied in the model. The submission has mapped those therapies in DB03 that are not likely to be used in the Australian setting to medicines used in Australia.

Rx = therapy; SC = subcutaneous; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following ranges:

¹ < 500

- 6.38 An alternative base case (Table 11) has retained the distribution of subsequent therapies derived from DB03, but reduced usage so that patients cannot receive more than one subsequent therapy at a time (Table 9). This change to the modelled use of subsequent therapies has a marked impact on the ICER. It was clarified by the sponsor in pre-PBAC response that it considered it appropriate to normalise the cost of subsequent anti-cancer therapies to 100% per cycle for each patient who receives subsequent therapies.
- 6.39 The key drivers of the model are presented in Table 10. The impact of key drivers is estimated by changing only that input. However, the impact may change markedly if multiple re-specifications are implemented. The ESC also considered the price of T-DXd to be a key driver of the economic model.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case ICER \$ ¹ /QALY
Extrapolation of OS	Dependent extrapolation of OS based on the Weibull parametric function.	High, favours T-DXd. Using independently fit Gamma for T-DXd and Weibull for T-DM1 results in an increase in the ICER to \$ ² per additional QALY. Applying no ongoing treatment effect from the point of data truncation results in an ICER of almost \$ ³ per additional QALY.
Extrapolation of PFS	Independent extrapolation of PFS based on log normal parametric functions for both T-DXd and T-DM1	Moderate, favours T-DXd. The log logistic parametric function has similar statistical fit parameters as the log normal parametric function for T-DXd. Using the log logistic function for T-DXd and log normal function for T-DM1, the ICER increases to \$ ² per additional QALY.
Subsequent anti-cancer therapies	29.9% of the T-DXd arm receives 197% utilisation of subsequent therapies. 62.4% of the T-DM1 arm receives 237% utilisation of subsequent therapies	Very high, favours T-DXd. Applying subsequent therapies to 100% of patients in the post-progression health state and calculating the cost of subsequent therapies per cycle based on patients receiving only one subsequent therapy at a time results in the ICER increasing to \$ ³ per additional QALY.

^a The ICER calculated includes the application of the ITT HR for both OS and PFS, and increasing ToT for the chemotherapy arm to match that of the mean treatment duration of docetaxel, paclitaxel and vinflunine. Changes to PFS and ToT do not have a marked impact on the model.

Source: Compiled during evaluation based on Section 3.9 of the submission.

HR = hazard ratio; ICER = incremental cost effectiveness ratio; ITT = intention to treat; OS = overall survival; QALY = quality of adjusted life year; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following ranges:

¹\$115,000 to < \$135,000

²\$135,000 to < \$155,000

³\$155,000 to < \$255,000

6.40 The ESC considered the ICER of the base case in the submission to be high and uncertain. The commentary proposed an alternative base case (Table 11) using a multivariate analysis, which the ESC considered to be an appropriate re-specified base case and noted that the ICER increased substantially with reasonable changes to model parameters. The PSCR estimated a median increase in PFS with T-DXd of 18.4 months. Based on the submission's base case, the modelled mean undiscounted increase in PFS was 28.5 months and the mean undiscounted gain in OS was 23.6 months, or 83% of the gain in PFS. Based on the evaluation's alternative base case the modelled mean undiscounted increase in PFS was 23.6 months and the mean undiscounted gain in OS was 10.4 months, or 44% of the gain in PFS.

Table 11: Model inputs altered from the base case in the alternative base case (multivariate analysis)

Description of change	Base case value	Alternative base case value	ICER (cumulative) (\$)	Change in ICER
Base case	-	-	1	0%
Correction of overall survival referencing error	1 cycle offset in determining overall survival	Corrected	1	+0.89%
Data truncation points for PFS and OS	15.5 months T-DXd 13.9 months T-DM1	18 months T-DXd 18 months T-DM1	1	+6.98%
Proportion of patients receiving subsequent therapies ^b	T-DXd: 29.9% T-DM1: 62.4%	T-DXd: 100% T-DM1: 100%	2	+25.26%
Quantity of post progression treatments applied each cycle ^{a, b}	T-DXd: 197% T-DM1: 237%	T-DXd: 100% T-DM1: 100%	2	+34.35%
Remove 6 months of subsequent treatments and post-progression management costs from end-of-life costs	\$49,977	\$27,107	2	+35.52%
Parametric function for extrapolation of PFS	T-DXd: independent log-normal T-DM1: independent log-normal	T-DXd: independent log-logistic T-DM1: independent log-normal	2	+49.39%
Parametric function for extrapolation of OS	T-DXd: dependent Weibull T-DM1: dependent Weibull	T-DXd: independent gamma T-DM1: independent Weibull	2	+84.34%

Source: generated during the evaluation.

ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

^aTable 9 explains the method used in the submission to estimate the quantity and type of subsequent therapies costed for each person who receives subsequent therapies.

^bFor each person who receives a subsequent therapy, the cost per cycle is \$[redacted] in the T-DXd arm, and \$[redacted] in the T-DM1 arm. When applied to the proportion expected to receive subsequent therapies (29.9% and 62.4% in the T-DXd arm and T-DM1 arm, respectively), the cost of subsequent therapies per cycle in the T-DXd arm is \$[redacted] and is \$[redacted] in the T-DM1 arm.

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$155,000 to < \$255,000

6.41 Results of the stepped economic evaluation are summarised in Table 12.

Table 12: Stepped analysis for the submission's base case and the evaluation's alternative base case

Base case	Cost			Outcomes			ICER
	T-DXd (\$)	T-DM1 (\$)	Inc. (\$)	T-DXd	T-DM1	Inc.	
Step 1: Trial-based analysis (19 months)				1.45	1.36	0.09	\$ ¹ /LY
Step 2: Extrapolation to 15-year time horizon				4.61	3.15	1.45	\$ ² /LY
Step 3: Inclusion of all costs				4.61	3.15	1.45	\$ ³ /LY
Step 4: Transformation to QALYs				3.33	2.00	1.34	\$ ³ /QALY
Alternative base case	Cost			Outcomes			ICER
	T-DXd (\$)	T-DM1 (\$)	Inc. (\$)	T-DXd	T-DM1	Inc.	
Step 1: Trial-based analysis (19 months) ^a				1.44	1.36	0.08	\$ ¹ /LY
Step 2: Extrapolation to 15-year time horizon				4.20	3.54	0.66	\$ ⁴ /LY
Step 3: Inclusion of all costs				4.20	3.54	0.66	\$ ⁴ /LY
Step 4: Transformation to QALYs				3.05	2.22	0.82	\$ ⁵ /QALY

^aThe only impact of the alternative base case on Step 1 is to correct the overall survival calculation error. This has the effect of removing the inappropriate 3 week (1 cycle) delay in the OS curve for T-DXd. The T-DM1 curve does not have this error.

Source: Table 3.22, p150 of the submission. Alternative base case generated during the evaluation based on the economic evaluation spreadsheet.

ICER = incremental cost effectiveness ratio; Inc. = incremental; QALYs = quality adjusted life years; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$135,000 to < \$155,000

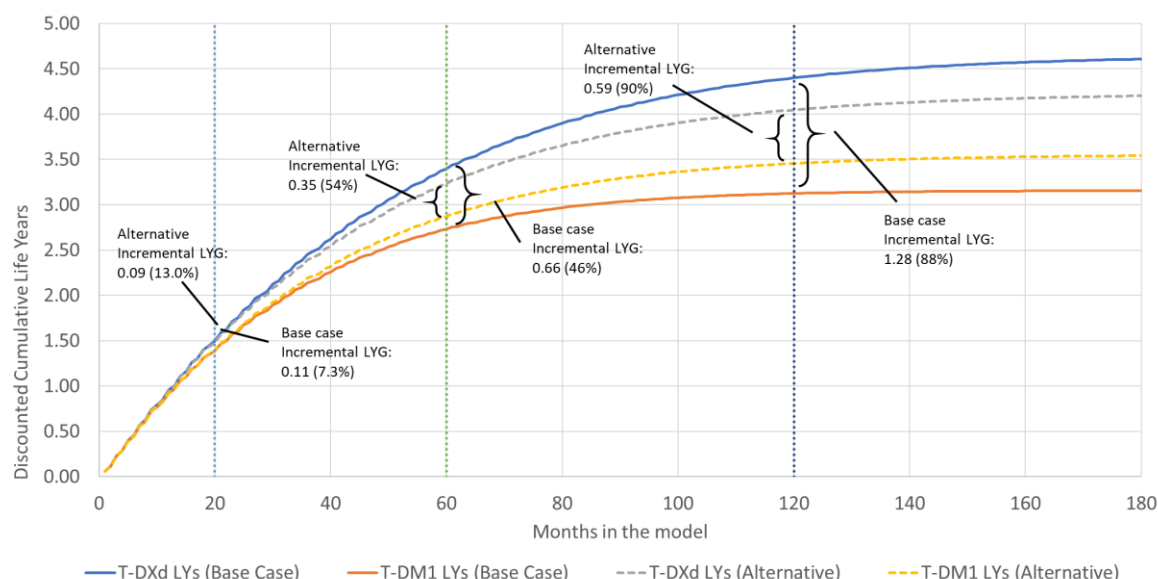
³ \$115,000 to < \$135,000

⁴ \$255,000 to < \$355,000

⁵ \$155,000 to < \$255,000

6.42 Approximately 20 months of observed trial data from DB03 is applied within the model. The model with a 15 year time horizon relies on an extrapolation period in which more than 90% of the total life years are gained with T-DXd versus T-DM1 (Figure 8). Most of these gains occur prior to 10 years in the model, with the final 5 years only adding approximately 12% to the life years gained with T-DXd versus T-DM1.

Figure 8: Accrual of life year gains (discounted) over time in the model, by treatment arm, for the base case and alternative base case



Source: generated during the evaluation from the economic evaluation spreadsheet
LYG = life years gained; LYs = life years; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

6.43 The submission presented univariate sensitivity analyses relating to costs, utilities, extrapolations, time horizon and discounting. Apart from the use of subsequent anti-cancer therapies, the base case is reported to not be particularly sensitive to univariate changes in the parameters included in the sensitivity analyses. Table 13 shows the discounting analyses for 5%, 3.5% and 0%.

Table 13: Results of the sensitivity costs and benefits discounting analyses for the submission base case and the commentary alternative base case

	Base case			Commentary alternative base case		
	Incremental costs (\$)	Incremental QALYs	ICER (\$/QALY)	Incremental costs (\$)	Incremental QALYs	ICER (\$/QALY)
Base case (5%)		1.34	¹		0.82	³
SA (3.5%)		1.44	¹		0.88	³
SA (0%)		1.74	²		1.04	³

Source: Table 3.25, pp153-4 of the submission. Alternative base case generated during the evaluation from the economic evaluation spreadsheet.

ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SA = sensitivity analysis.

The redacted values correspond to the following ranges:

¹\$115,000 to < \$135,000

²\$95,000 to < \$115,000

³\$155,000 to < \$255,000

Drug cost/patient/course

6.44 The dose and duration of treatment for T-DXd are consistent across the economic model and financial estimates. The slightly shorter duration of treatment in the

financial estimates relate to the truncation of the time on treatment curve. The mean duration of treatment for T-DXd in DB03 is 13.7 months and has been extrapolated using a generalised gamma function for both the model and financial estimates (Table 14).

- 6.45 The comparator for the DB03 trial, and used in the economic model, is T-DM1. The financial estimates include trastuzumab subcutaneous, lapatinib and capecitabine as therapies that will be replaced, and therefore the mean dose, duration and costs are not comparable with the economic model (Table 14).

Table 14: Drug cost per patient for trastuzumab deruxtecan and trastuzumab emtansine (excluding administration costs)

	Proposed drug - Trial dose and duration	Proposed drug - Economic model	Proposed drug - Financial estimates	Comparator - Trial dose and duration	Comparator - Economic model	Comparator - Financial estimates ^d
Mean dose/cycle	314mg ^b	357.6mg ^a	4 vials	210.8mg ^c	247.2mg	various
Mean duration	13.7 months	27.4 months	24.8 months ^e	8.0 months	12.3 months	-
Cost/patient/month	-	\$	\$ ^f	-	\$	-
Cost/patient/course	-	\$	\$ ^f	-	\$	-

Source: Table 10.1, pp107-8 of the CSR; Table 14.1.5.1.1 of the CSR, Model estimates generated from the economic model.

a Estimated using Australian weight of 71.9kg, and 92.1% relative dose intensity for T-DXd and 95.5% relative dose intensity for T-DM1.

b Cannot be located in the CSR. Has been calculated by multiplying 5mg/kg/cycle (average dose) by 62.8kg (average weight in T-DXd arm).

c Cannot be located in the CSR. Has been calculated by multiplying 3.4mg/kg/cycle (average dose) by 62kg (average weight in T-DM1 arm).

d The comparator for the financial estimates include T-DM1, trastuzumab sub-cutaneous, lapatinib and capecitabine.

e The duration of treatment in the financial section is drawn from a truncated extrapolation of DB03, and is applied to most (but not all) of the population. Treatment duration following long term trastuzumab monotherapy is 33.77 weeks.

f Estimated by converting the effective price (\$) per cycle to a per month cost (divide by 21 days, multiply by 365.25 and divide by 12 months). Cost is duration multiplied by effective price per month.

- 6.46 The doses of both T-DXd and T-DM1 in the DB03 trial were lower than is anticipated in the Australian setting. This is because the dosing of T-DXd and T-DM1 are weight based, and the patient weight in DB03 was considerably less (62 to 63 kg) than the target Australian population (71.9 kg). The Australian weight is based on the mean weight of patients in the 2nd line treatment setting and was estimated from an IPSOS clinician survey. The model has appropriately estimated the cost of T-DXd and T-DM1 based on doses required for the estimated weight of the Australian population.
- 6.47 The cost per patient per course should not be estimated from the trial, as patients remain on treatment.

Estimated PBS usage & financial implications

- 6.48 This submission was considered by DUSC.
- 6.49 Key inputs for financial estimates are shown in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Total 1L HER2 mBC	Back calculated from the PBS prescriptions of pertuzumab (assuming 85% of all patients are treated with pertuzumab), inflated by 5% per year. Estimated to be █████ ¹ in Year 1, increasing to █████ ¹ in Year 6. 85% are assumed to be eligible for 2L treatment.	The financial implications are sensitive to the number of patients. Changes to the estimate of pertuzumab use in HER2 mBC patients, or the proportion remaining eligible for 2L therapy, will markedly impact the financial estimates.
Additional patients from long term trastuzumab monotherapy use	Assumption. Estimated to be █████ ² in Year 1 and zero in subsequent years.	This estimate is uncertain, however has a limited effect on ongoing financial implications.
Uptake rate	█████% in Year 1 increasing to █████% in Year 3+. Assumption, based on clinician input.	
Grandfathered patients	Grandfathered patients are assumed to be captured by the approach taken to estimate the incident population.	
Dose/duration	Based on duration of treatment in DB03, extrapolated using generalized gamma to 6 years. Treatment duration is truncated at 6 years. Duration of treatment following long term trastuzumab monotherapy is estimated at 33.77 months.	This is consistent with the economic evaluation. Truncation will not impact the financial estimates within the 6-year timeframes.
Offsets for therapies to be replaced	Key offsets include T-DM1 (duration of treatment derived from DB03), trastuzumab sub-cutaneous, lapatinib and capecitabine.	The economic model only compared against T-DM1. As T-DM1 is more costly than other comparators, including alternative treatments as offsets in Section 4 will result in a higher estimated financial impact of T-DXd.
MBS 13950	The only MBS item included relates to administration costs of the medicine.	The economic model includes a number of MBS items relating to management and monitoring. These are similar across the arms and including them is not likely to impact the estimates from Section 4.

Source: Table 4.1, p157 of the submission.

DB03 = DESTINY Breast 03 trial; HER2 = human epidermal growth factor receptor 2; mBC = metastatic breast cancer; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

6.50 The financial implications of listing T-DXd are presented in Table 16.

Table 16: Estimated use and financial implications (based on proposed effective price of T-DXd)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	¹	¹	¹	¹	¹	¹
Number of scripts dispensed ^a	²	²	³	³	³	⁴
Estimated financial implications of T-DXd						
Cost to PBS/RPBS less copayments (\$)	⁵	⁵	⁵	⁶	⁶	⁶
Estimated financial implications for T-DM1, trastuzumab sub-cutaneous, lapatinib and capecitabine						
Cost to PBS/RPBS less copayments (\$)	⁷	⁸	⁹	⁹	⁹	¹⁰
Net financial implications						
Net cost to PBS/RPBS (\$)	¹¹	⁵	⁵	⁵	⁵	⁵
Net cost to MBS (\$)	¹²	¹²	¹²	¹²	¹²	¹²

Source: Table 4.14, p175, Table 4.15, p175, Table 4.17, p176, Table 4.24, p179, Table 4.27, p181 of the submission.

^a Scripts are estimated based on duration of treatment. Patients who continue treatment into a subsequent year contribute to scripts in that subsequent year.

MBS = Medicare Benefits Schedule; (R)PBS = (Repatriation) Pharmaceutical Benefits Scheme; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following ranges:

¹500 to < 5,000

²10,000 to < 20,000

³20,000 to < 30,000

⁴30,000 to < 40,000

⁵\$100 million to < \$200 million

⁶\$200 million to < \$300 million

⁷\$20 million to < \$30 million

⁸\$30 million to < \$40 million

⁹\$40 million to < \$50 million

¹⁰\$50 million to < \$60 million

¹¹\$80 million to < \$90 million

¹²\$0 to < \$10 million

- 6.51 The net cost to the PBS/RPBS of listing trastuzumab deruxtecan was estimated to be \$80 million to < \$90 million in year 1, and a total of \$800 million to < \$900 million in the first 6 years of listing.
- 6.52 The estimated financial impact is sensitive to the incidence of patients with HER2 positive mBC. The submission has used the current uptake of pertuzumab in first-line HER2 positive mBC to estimate the number of patients that would be eligible for second-line treatment.
- 6.53 The financial impact is not consistent with the economic model in terms of the assumed cost-offsets. The economic model assumes ongoing treatment with subsequent therapies post-progression until death. The financial model includes a single line of therapy (either T-DXd or one of T-DM1, trastuzumab sub-cutaneous or lapatinib plus capecitabine). Excluding subsequent lines of therapy may affect the financial impact. Subsequent therapies for T-DXd will include T-DM1, which is the most costly alternative medicine. Including subsequent therapies following those that are costed as offsets will extend costing for a greater duration of time.

- 6.54 The estimated financial impact may also be sensitive to the duration of treatment of T-DXd. If the use of T-DXd were limited to 2 years, the cost to the PBS/RPBS would be reduced from \$200 million to < \$300 million in Year 6 to \$100 million to < \$200 million.
- 6.55 Grandfathered patients are expected to be captured using the method for estimating incident patients.
- 6.56 The DUSC considered the estimates presented in the submission to be underestimated.
- 6.57 The DUSC considered that prevalent patient data suggested that the number of pertuzumab patients was yet to plateau. The DUSC noted that the number of pertuzumab patients in quarter three of 2021 was 1,247 and the number of T-DM1 patients prior to the restriction change for early breast cancer in quarter two of 2020 was 300. The DUSC considered that this suggested a possible eligible population of 1,547. While assuming 85% of patients experience progression there may be up to 500 to < 5,000 patients eligible for treatment with T-DXd. The DUSC also considered that there was uncertainty with this method of estimating an eligible population as there is uncertainty in when the growing population of pertuzumab patients will progress to second-line.
- 6.58 The DUSC noted that the submission assumed subsequent lines of therapy would be replaced by T-DXd. However, the DUSC agreed with the evaluation and considered it was more likely that these therapies would be displaced downstream in the treatment algorithm and noted that the cost offsets will likely not be as significant as proposed in the submission.
- 6.59 The DUSC agreed with the evaluation that due to the long treatment duration with T-DXd and the time taken to reach maximum market share, the financial estimates in Year 6 would be expected to continue to increase. The DUSC noted the growing pertuzumab population was indicative of what may occur with T-DXd.

Quality Use of Medicines

- 6.60 The submission has presented information relating to the availability of a guide for health care practitioners and a patient card. These materials are intended to reduce the likelihood of interstitial lung disease and pneumonitis.
- 6.61 The sponsor stated in the pre-PBAC response that it plans to run national pharmacist and nursing training meetings at the time of listing in order to provide information on the clinical background, safety profile and dosing and administration of T-DXd. It was stated that all training with prescribers, pharmacists, and nurses will be recorded by the sponsor and included in reports submitted to the TGA.

Financial Management – Risk Sharing Arrangements

- 6.62 The sponsor has stated that it is willing to work with PBAC and the Department of Health to determine appropriate terms for listing that share the risk of uncertainty

between the Sponsor and the Department. No details of any proposed risk sharing arrangements was included in the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend trastuzumab deruxtecan (T-DXd) for the treatment of human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer (mBC) for patients who have progressed following a prior HER2 directed therapy in the metastatic setting or relapsed during or within 6 months of receiving a HER2 directed therapy in the adjuvant setting.
- 7.2 The PBAC considered the evidence presented demonstrated substantial clinical benefit in PFS that is likely to translate into clinically meaningful gains in OS. The PBAC considered that the ICER presented in the submission was unacceptably high and likely underestimated due to an optimistic extrapolation. The PBAC considered a substantial price reduction would be required for T-DXd to be considered cost-effective. The PBAC also considered that the number of patients likely to be treated was overestimated, and that the financial impact was extremely high at the proposed price.
- 7.3 The PBAC noted the consumer comments highlighting an unmet clinical need for effective new therapy options for patients with HER2 positive mBC. The PBAC noted the comments highlighted the substantial PFS benefit associated with T-DXd therapy compared to T-DM1, as shown in the DB03 trial, and the quality of life benefits gained by reducing the burden associated with the fear of cancer recurrence and early death.
- 7.4 The PBAC considered that the requested written authority listing for initial therapy with T-DXd was not required and that a telephone/online PBS authority for T-DXd would be appropriately in line with the restriction type for T-DM1. The PBAC noted that the requested restriction included patients with rapid relapse during or within 6 months of adjuvant treatment with a HER2 directed therapy; however, patients who had received adjuvant therapy with T-DM1 were excluded from the DB03 trial as they could not ethically be randomised to another line of T-DM1. This patient group represents a small percentage of HER2 positive breast cancer patients who remain at high risk of a recurrence, and the use of T-DXd in these patients is supported by the DB01 trial. Therefore the PBAC advised a restriction including this patient population was reasonable.
- 7.5 The PBAC considered the nominated comparator, trastuzumab emtansine (T-DM1), to be appropriate.
- 7.6 The primary clinical evidence supporting the clinical claim was the DB03 clinical trial (N=524) comparing T-DXd with T-DM1. The PBAC noted treatment with T-DXd was associated with a significant increase in PFS compared with T-DM1 (HR 0.28. 95% CI 0.22, 0.37) and noted that median PFS had not been reached in the T-DXd arm. The

PBAC also noted that the clinical benefit did not appear to vary by subgroup. The PBAC noted that OS data were immature, however considered that the treatment benefit in PFS was likely to translate into clinically meaningful gains in OS.

- 7.7 The PBAC considered the claim of non-inferior safety was not adequately supported by the data. The PBAC noted that T-DXd was associated with increased gastrointestinal and haematological side effects compared with T-DM1 and highlighted that pneumonitis was a side effect of particular interest as its monitoring and treatment is often clinically intensive. The PBAC noted that T-DXd was associated with significantly more drug disruptions and dose reductions and considered that this was likely due to its inferior toxicity profile compared with T-DM1. Overall, the PBAC considered T-DXd demonstrated inferior safety compared with T-DM1, however considered the side effects associated with T-DXd manageable with an appropriate QUM arrangement.
- 7.8 The PBAC agreed with the ESC that the extrapolated gain in PFS and OS for T-DXd was overestimated in the economic model due to following issues:
- The data truncation points applied to the economic model favoured T-DXd, as the latter half of the PFS and OS KM curves appear to be less favourable to T-DXd than the initial 10 months. It was considered that a truncation point of 18 months was more appropriate.
 - The submission nominated the most favourable PFS extrapolation for the T-DXd arm. The log-logistic parametric function was considered to be the preferred extrapolation for T-DXd PFS, as it better reflects the end of the observed KM data.
 - The submission dependently fit a Weibull parametric function to the OS curves, which assumes a constant treatment effect. It was considered that this assumption was not supported by the available DB03 trial data, and that the preferred extrapolations for OS are an independently fitted gamma function for the T-DXd arm and an independently fitted Weibull function for the T-DM1 arm.
- 7.9 The PBAC noted that the Sponsor accepted recommendations from the evaluation and the ESC to modify model inputs for subsequent anti-cancer therapies. This included: (1) removing 6 months of subsequent anti-cancer therapy costs and 6 months of disease management costs from the end-of-life costs to avoid double counting; (2) increasing the proportion of patients in each arm with progressive disease who would receive subsequent anti-cancer therapies to 100% rather than a reduced fraction; and (3) normalising the cost of subsequent anti-cancer therapies to 100% per cycle for each patient who receives subsequent therapies so that patients cannot receive more than one anti-cancer therapy at a time.
- 7.10 The PBAC considered that the ICER of \$95,000 to < \$115,000 /QALY gained for the submission's base case was unacceptably high and optimistic. The PBAC noted that this ICER was sensitive to the OS and PFS extrapolations and the cost of subsequent anti-cancer therapies. The PBAC noted that when the changes outlined in paragraphs

7.8 and 7.9 were applied the ICER increased to \$155,000 to < \$255,000/QALY gained. The PBAC considered a substantial reduction in the cost of T-DXd would be required for it to be considered cost-effective. The PBAC advised that an ICER of below \$75,000/QALY gained would be consistent with treatments for mBC previously considered by PBAC.

7.11 The PBAC considered the financial estimates presented in the submission were overestimated. The PBAC noted that the DUSC considered that when assuming 85% of patients experience progression on first-line treatment there may be up to 500 to < 5,000 patients eligible for treatment with T-DXd. However, the PBAC considered that 85% was an overestimate of the percentage of patients likely to experience progression on first-line treatment during the forecasted financial period. The PBAC considered that the number of patients eligible for treatment with T-DXd in the second-line setting was likely to align with the number of patients initiating T-DM1 therapy. The PBAC advised that these estimates should be in addition to:

- a small pool of patients who relapse during or within 6 months of adjuvant HER2 directed treatment.
- a prevalent pool of patients currently receiving second-line T-DM1, assuming 85% of patients are expected to progress to third-line T-DXd during the first and second year of treatment.
- a small prevalent pool of patients receiving third-line and later-line therapies, who are expected to progress during the first year of treatment.

7.12 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for T-DXd. The PBAC also considered T-DXd addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- amend economic model to address the overestimated extrapolated gain in PFS and OS, as outlined in paragraph 7.8;
- amend the cost and likelihood of subsequent anti-cancer therapies in the economic model, as recommended by the evaluation;
- a reduction in the cost of T-DXd so that the resulting ICER is below \$75,000/QALY gained; and
- revised financial estimates to include a lower - T-DXd cost and revision to the eligible patient population, as outlined in paragraph 7.11.

7.13 The early resolution resubmission must be lodged by Week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple

resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the July 2022 PBAC PSD:

**7.03 TRASTUZUMAB DERUXTECAN,
Powder for I.V. infusion 100 mg,
Enhertu[®],
AstraZeneca Pty Ltd.**

10 Background

- 10.1 The resubmission requested a Section 100, Authority Required listing for trastuzumab deruxtecan (T-DXd; Enhertu[®]) for the treatment of human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer (mBC) for patients who have progressed following a prior HER2 directed therapy in the metastatic setting, or relapsed during or within 6 months of receiving a HER2 directed therapy in the adjuvant setting.
- 10.2 At the July 2022 PBAC meeting, T-DXd was not recommended for the requested listing. The resubmission was made under the early resolution pathway and sought to address the PBAC's concerns from its July 2022 meeting. The PBAC considered that the following changes may address the outstanding issues without requiring re-evaluation:
- Amend the economic model to address the overestimated extrapolated gain in progression free survival (PFS) and overall survival (OS) (paragraph 7.8);
 - Amend the cost and likelihood of subsequent anti-cancer therapies in the economic model (paragraph 7.9);
 - Reduce the cost of T-DXd so that the resulting incremental cost effectiveness ratio (ICER) is below \$75,000 per quality adjusted life year (QALY) gained (7.10); and
 - Revise the financial estimates to include a lower T-DXd cost and revise the eligible patient population (paragraph 7.11).
- 10.3 Table 17 summarises how the resubmission addressed each of these issues. Table 17 also shows some additional revisions that were made in the resubmission that were not requested by the PBAC, in relation to the requested listing and clinical data. Further additional revisions to the economic model and financial impact in the resubmission are not shown in Table 17 as they lie outside the intention of the July 2022 early resolution recommendation.

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

Table 17: Summary of changes made in the resubmission

PBAC PSD recommended change July 2022	Early resolution resubmission change December 2022	Addressed?
Requested listing		
NR	The resubmission provided updated proposed PBS restriction wording to align with the population described by the PBAC in the PSD (paragraph 7.11) from the July 2022 PBAC meeting.	The population described by the PBAC in paragraph 7.11 was intended for adjustment of the financial estimates, not the proposed restriction.
Comparative effectiveness and safety		
NR	The resubmission presented updated efficacy (PFS and OS) and safety data from the pivotal trial DB03 (IA2).	Updated efficacy data informed the magnitude of benefit claimed for T-DXd compared with T-DM1. Updated safety data informed the claim that all observed AEs associated with T-DXd are known and manageable. However, the resubmission did not revise the July 2022 non-inferiority claim and thus it was not aligned with the PBAC's July 2022 finding of inferior but manageable safety.
Economic model		
Amend the economic model to address the overestimated extrapolated gain in PFS and OS (paragraph 7.8): - It was considered that a truncation point of 18 months for PFS and OS was more appropriate. - The log-logistic parametric function was considered to be the preferred extrapolation for T-DXd PFS, as it better reflects the end of the observed KM data. - The preferred extrapolations for OS are an independently fitted gamma function for the T-DXd arm and an independently fitted Weibull function for the T-DM1 arm.	The resubmission retained the extrapolation functions from the July 2022 model for PFS and OS. The resubmission stated that the data truncation for PFS and OS curves was adjusted to the point where 20% of patients remain at risk of an event: PFS, 30 months for T-DXd and 18 months for T-DM1; OS, 34 months for T-DXd and 33 months for T-DM1.	No. Without further evaluation of the model, the parametric functions for PFS and OS as recommended in July 2022 should be used. The December 2022 model extended the truncation points in line with the updated efficacy data from IA2 of the DB03 trial, which was beyond the 18 months recommended by the PBAC for IA1. The use of IA2 data may support extrapolation from a point beyond 18 months.
Amend the cost and likelihood of subsequent anti-cancer therapies in the economic model (paragraph 7.9).	The Sponsor accepted these recommendations in their PSCR and pre-PBAC response prior to the July 2022 meeting.	Yes
Reduce the cost of T-DXd so that the resulting ICER is below \$75,000/QALY gained (paragraph 7.10).	The resubmission proposed an effective price for T-DXd of \$[REDACTED] per vial,	No. This ICER is higher than that proposed in the PBAC PSD, using OS and

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

PBAC PSD recommended change July 2022	Early resolution resubmission change December 2022	Addressed?
	reduced from \$ [redacted] per vial in the July 2022 submission, a [redacted] % reduction. The resubmission stated that the price reduction drives a decrease in the ICER from \$ [redacted] ¹ to \$ [redacted] ² /QALY.	PFS extrapolation and amendments to other model inputs not aligned with the PBAC's advice from July 2022.
Financial estimates		
Revise the financial estimates to include a lower T-DXd cost and revision to the eligible patient population (paragraph 7.11).	The resubmission stated that it provided updated patient numbers and financial estimates based on the PBAC's recommendations, as well as information shared with the Sponsor by the DUSC Secretariat.	No. The financial estimates did not align with the advice from the PBAC in July 2022.
Risk sharing arrangements		
NR	The resubmission requested a Deed of Agreement that is exclusive to T-DXd and acknowledged areas of budget impact risk for both the Government and the Sponsor.	No. Underpinning financial estimates require revision.

AEs = adverse events; DB03 = DESTINY-Breast 03; IA2 = Interim Analysis 2; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; NR = not requested; OS = overall survival; PFS = progression free survival; PSCR = Pre-Sub-Committee Response; PSD = Public Summary Document; QALY = quality adjusted life year; SoC = standard of care; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following ranges:

¹\$115,000 to < \$135,000

²\$75,000 to < \$95,000

11 Requested listing

- 11.1 The PBAC did not request changes to the requested restriction criteria reviewed by the PBAC at the July 2022 meeting.
- 11.2 In July 2022, the PBAC considered that the requested written authority level for initial therapy with T-DXd was not required and that a telephone/online PBS authority level for T-DXd would be appropriately in line with the restriction type for trastuzumab emtansine (T-DM1). The PBAC also advised that a restriction including patients with rapid relapse during or within 6 months of adjuvant treatment with a HER2 directed therapy was reasonable.
- 11.3 The resubmission stated that the PBAC provided advice regarding limiting initiations to T-DXd from prevalent T-DM1 patients (to 2 years) and prevalent trastuzumab patients (to 1 year), to minimise the risk of any use in these populations after these periods of time. The PBAC noted that advice in paragraph 7.11 of July 2022 PSD regarding prevalent patients was provided for adjustment of the financial estimates, and was not intended to be applied to the restriction.

11.4 The resubmission:

- Reiterated the request for the initial script for T-DXd to be a written authority to ameliorate the risk of use outside the restriction;
- Added to the initial therapy clinical criterion that patients must have progressed during or within 6 months following adjuvant treatment with a HER2 directed therapy *as the most recent therapy*;
- Replaced the initial therapy clinical criterion that “The condition must have progressed following treatment with at least one prior HER2 directed regimens for metastatic breast cancer” with three criteria that were stated to minimise the risk of use beyond 2 years for patients transitioning from T-DM1 and 1 year for patients transitioning from trastuzumab.⁸

For more detail on PBAC’s view, see section 13 PBAC outcome.

12 Consideration of the evidence

- 12.1 As an early resolution resubmission, the updated clinical evidence has not been independently evaluated.

Consumer comments

- 12.2 In addition to the input noted by the PBAC at the July 2022 meeting (see paragraphs 6.2 to 6.5), the PBAC noted and welcomed the input from an organisation via the Consumer Comments facility on the PBS website.
- 12.3 The advice received from the Breast Cancer Network Australia (BCNA) supported the PBS listing of T-DXd for the treatment of HER2 positive mBC. The BCNA noted that the delay in recommending subsidy has considerable implications for patients, including the financial burden of private funding, reduced equity of access, and prolonged psycho-social distress.

⁸ The 3 criteria were: (1) “The condition must have progressed following treatment with pertuzumab and trastuzumab in combination as the most recent therapy in the metastatic setting” OR (2) “The condition must have progressed following treatment with trastuzumab emtansine as the most recent therapy in the metastatic setting” (to be removed after 2 years) OR (3) “Initial treatment for patients transitioning from trastuzumab initiated prior to [Date of PBS listing] to PBS-subsidised treatment – temporary arrangements – Patient must have progressed following treatment with at least two prior HER2 directed therapies in the metastatic setting; AND The most recent treatment (during which the condition progressed) was trastuzumab” (to be removed after 1 year).

Comparative effectiveness

- 12.4 The July 2022 submission presented data from Interim Analysis 1 (IA1) of the DESTINY-Breast 03 (DB03) trial, conducted 21 May 2021. The resubmission presented updated data from Interim Analysis 2 (IA2) of the DB03 trial, conducted 25 July 2022.
- 12.5 At IA1 (21 May 2021), treatment with T-DXd resulted in a statistically significant and clinically meaningful improvement in PFS as assessed by blinded independent central review (BICR), corresponding to a 72% reduction in the overall risk of progression or death compared to T-DM1 (hazard ratio [HR]=0.28; 95% CI 0.22, 0.37; $P < 0.000001$) (paragraph 7.6). The median PFS by BICR was not reached for subjects receiving T-DXd, compared to 6.8 months for subjects receiving T-DM1 (Table 18 and Figure 9).
- 12.6 The resubmission stated that at IA2 (25 July 2022), T-DXd continued to demonstrate a statistically significant and clinically meaningful improvement in PFS, corresponding to a 67% reduction in the overall risk of progression or death compared to T-DM1 (HR=0.33; 95% CI 0.26, 0.43; $p < 0.000001$) (Table 18 and Figure 9). The median PFS by BICR was reached: 28.8 months (95% CI 22.4, 37.9) for subjects receiving T-DXd, compared with 6.8 months (95% CI 5.6, 8.2) for subjects receiving T-DM1.

Table 18: Analysis of PFS based on BICR from IA1 and IA2 of the DESTINY-Breast 03 trial

	IA1 (July 2022 PBAC consideration)		IA2 (December 2022 resubmission)	
	T-DXd N=261	T-DM1 N=263	T-DXd N=261	T-DM1 N=263
Median PFS by BICR (months) ^a	NR	6.8	28.8	6.8
95% CI	18.5, NE	5.6, 8.2	22.4, 37.9	5.6, 8.2
Hazard ratio	0.28		0.33	
95% CI	0.22, 0.37		0.26, 0.43	
Stratified log-rank nominal p-value ^b	p < 0.000001		p < 0.000001	
Subjects (%) with events	87 (33.3)	158 (60.1)	117 (44.8)	171 (65.0)
Progressive disease	80 (30.7)	152 (57.2)	108 (41.4)	164 (62.4)
Death	7 (2.7)	6 (2.3)	9 (3.4)	7 (2.7)
Subjects (%) without events (censored)	174 (66.7)	105 (39.9)	144 (55.2)	92 (35.0)

BICR = blinded independent central review; CI = confidence interval; IA1 = Interim Analysis 1; IA2 = Interim Analysis 2; NE = not estimable; NR = not reached; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

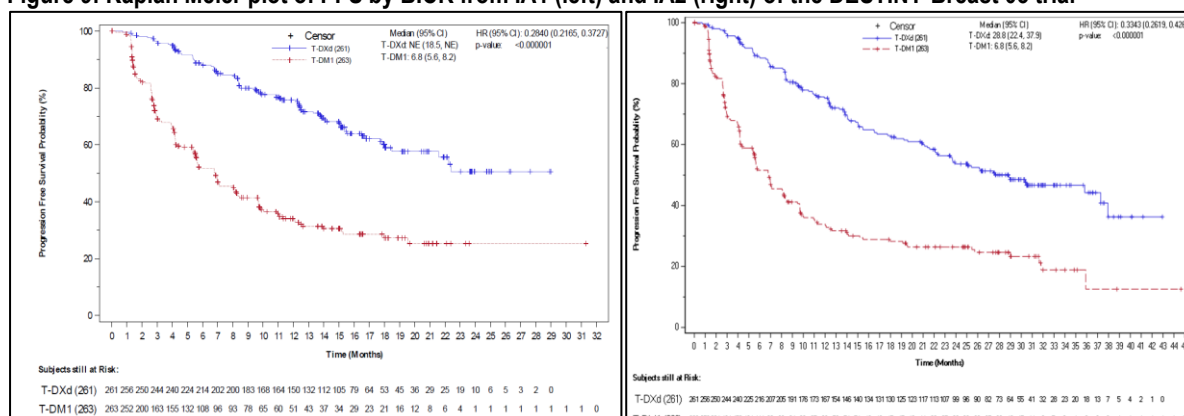
Statistically significant results in **bold**.

^a Median PFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.

^b Two-sided p-value from stratified log-rank test, hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factors.

Source: Resubmission Table 2.3-1.

Figure 9: Kaplan Meier plot of PFS by BICR from IA1 (left) and IA2 (right) of the DESTINY-Breast 03 trial



BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; IA1 = interim analysis 1; IA2 = interim analysis 2; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan. HR is from the stratified Cox proportional hazard model; *P*-value is from the stratified log-rank test.

Source: Resubmission Figures 2.3-1 and 2.3-2.

12.7 At IA2, T-DXd statistically significantly reduced the risk of death compared with T-DM1 with 72 (27.6%) deaths in the T-DXd arm compared with 97 (36.9%) deaths in the T-DM1 arm, a reduction in the risk of death of 36% (HR=0.64; [95% CI 0.47, 0.87]; $p=0.0037^9$). This compares to a HR of 0.55 (95% CI 0.36, 0.86) for IA1 (Table 19 and Figure 10). The resubmission stated that due to the commercial availability of T-DXd in some markets, there were 42 patients (16% of total patients) in the T-DM1 arm who crossed over to receive T-DXd post progression, which may have impacted the OS results in favour of T-DM1.

⁹ The *p*-value required to claim statistical significance in the DB03 trial for IA2 OS was 0.013 (α boundary). The boundaries and the power were recalculated at OS IA2 based on the actual number of OS events observed.

Table 19: Analysis of OS from IA1 and IA2 of the DESTINY-Breast 03 trial

	IA1 (July 2022 PBAC consideration)		IA2 (December 2022 resubmission)	
	T-DXd N=261	T-DM1 N=263	T-DXd N=261	T-DM1 N=263
Subjects (%) with events (deaths)	33 (12.6)	53 (20.2)	72 (27.6)	97 (36.9)
Subjects (%) without events (censored)	228 (87.4)	210 (79.8)	189 (72.4)	166 (63.1)
Alive	215 (82.4)	192 (73.0)	170 (65.1)	138 (52.5)
Lost to follow-up	13 (5.0)	18 (6.8)	19 (7.3)	28 (10.6)
Hazard ratio	0.55^d		0.64	
95% CI	0.36, 0.86^d		0.47, 0.87^d	
Stratified log-rank p-value ^a	p = 0.0072^d		p = 0.0037^d	
Median OS (months) ^b	NE	NE	NE	NE
95% CI	NE (NE, NE)	NE (NE, NE)	(40.5, NE)	(34.0, NE)
OS Rate at 12 Months (95% CI) ^c	94.1 (90.3, 96.4)	85.9 (80.9, 89.7)	94.1 (90.4, 96.4)	86.0 (81.1, 89.8)
OS Rate at 24 Months (95% CI) ^c	80.8 (73.0, 86.6)	73.7 (66.1, 79.9)	77.4 (71.7, 82.1)	69.9 (63.7, 75.2)
OS Rate at 36 Months (95% CI) ^c	N/A	N/A	69.3 (62.5, 75.1)	55.4 (47.4, 62.8)

CI = confidence interval; IA1 = Interim Analysis 1; IA2 = Interim Analysis 2; NE = not estimable; OS = overall survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Statistically significant results in **bold**.

^a Two-sided p-value from stratified log-rank test, Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factors.

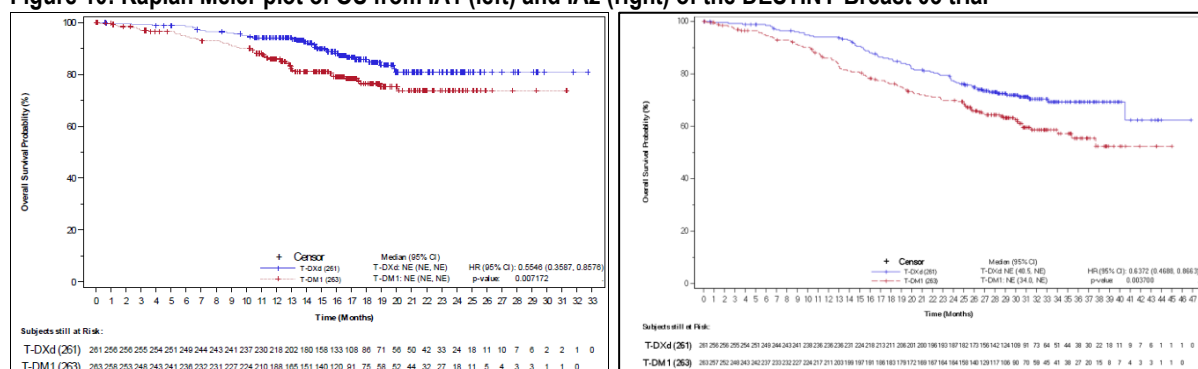
^b Median OS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.

^c Estimate and CI for OS rate at the specified time point are from Kaplan-Meier analysis.

^d The tabulated numbers for HRs, CIs and P-values in resubmission Table 2.3-2 do not match the text for IA2 in the resubmission on p25 or the IA1 data from the July 2022 submission (Table 4). Numbers shown in Table 19 are from resubmission text (IA2, p25) and from the July 2022 submission (IA1, Table 4).

Source: ResubmissionTable 2.3-2 and text p25.

Figure 10: Kaplan Meier plot of OS from IA1 (left) and IA2 (right) of the DESTINY-Breast 03 trial



CI = confidence interval; HR = hazard ratio; IA1 = interim analysis 1; IA2 = interim analysis 2; NE = not estimable; OS = overall survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

HR is from the stratified Cox proportional hazard model; P-value is from the stratified log-rank test.

Source: Figure 4 (July 2022 PSD) and resubmission Figure 2.3-4.

12.8 The resubmission stated that the overall response rate for subjects treated with T-DXd was close to 80%, compared to 35% for subjects receiving T-DM1, with 21.1% of subjects treated with T-DXd experiencing a complete response compared to 9.5% of subjects receiving T-DM1 (Table 20).

Table 20: ORR by BICR from IA1 and IA2 of the DESTINY-Breast 03 trial

Parameter	IA1 (July 2022 PBAC consideration)		IA2 (December 2022 resubmission)	
	T-DXd N = 261	T-DM1 N = 263	T-DXd N = 261	T-DM1 N = 263
Confirmed ORR, n (%)	208 (79.7)	90 (34.2)	205 (78.5)	92 (35.0)
95% CI	74.3-84.4	28.5-40.3	73.1-84.4	29.2-41.1
Difference in ORR p-value	45.5% (95% CI: 37.6, 53.4) p <0.0001		43.5% (95 % CI: 35.6, 51.6) p <0.0001	
Best Objective Response, n (%)				
CR	42 (16.1)	23 (8.7)	55 (21.1)	25 (9.5)
PR	166 (63.6)	67 (25.5)	150 (57.5)	67 (25.5)
SD	44 (16.9)	112 (42.6)	47 (18.0)	110 (41.8)
PD	3 (1.1)	46 (17.5)	3 (1.1)	47 (17.9)
Not evaluable	6 (2.3)	15 (5.7)	6 (2.3)	14 (5.3)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; HR = hazard ratio; IA1 = Interim Analysis 1; IA2 = Interim Analysis 2; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Statistically significant results in **bold**.

Source: Resubmission Table 2.3-3.

- 12.9 The PBAC noted that a subgroup analysis of the DB03 trial by age (<65 vs ≥65 years) indicated a reduced benefit in patients ≥65 years for T-DXd over T-DM1 with respect to OS (n=106; HR=1.29; 95% CI: 0.65, 2.56), with a point estimate unfavourable to T-DXd, compared with patients <65 years (n=418; HR=0.54; 95% CI 0.39, 0.77). The PBAC noted from DUSC advice that 33% (580/1,172) of T-DM1 initiations over the period 2015-2021 were in the ≥65 years age group; in contrast, the median age of T-DXd patients in the DB03 trial was 54.5 years and only 19% (49/261) of patients were in the ≥65 years age group.

Comparative harms

- 12.10 The resubmission stated that the safety data from IA2, with a longer duration of follow up than IA1, confirms that T-DXd has a manageable safety profile, with no new safety signals observed.
- 12.11 The PBAC noted that the safety data from IA2 indicated a substantial increase in some adverse events with T-DXd, including nausea (T-DXd: 77% vs T-DM1: 30%), vomiting (52% vs 11%), diarrhoea (32% vs 8%), alopecia (40% vs 3%), and neutropenia (31% vs 12%). The PBAC noted that trial patients discontinued treatment due to pneumonitis (6% vs 1%), interstitial lung disease (5% vs 0.3%) and pneumonia (2% vs 0%) in the respective T-DXd and T-DM1 arms.

Clinical claim

- 12.12 The clinical claim from the July 2022 meeting was that T-DXd is superior in terms of effectiveness to T-DM1 and non-inferior in terms of safety (albeit with a different safety profile). The PBAC considered in July 2022 that despite the immaturity of the OS data at IA1, the effectiveness claim was adequately supported by the large effect of T-DXd on PFS (72% reduction in hazard of progression or death) (paragraph 6.17). It considered that T-DXd demonstrated inferior safety compared with T-DM1,

however considered the side effects associated with T-DXd manageable with an appropriate Quality use of Medicines (QUM) arrangement (paragraph 6.20).

- 12.13 While the resubmission did not specifically revise the clinical claim from July 2022, it stated that IA2 provided greater certainty in the longer-term outcomes for T-DXd, and demonstrated that T-DXd provides clinically and statistically significant gains in PFS and OS compared with T-DM1 for this patient population.
- 12.14 As per its July 2022 recommendation, the PBAC considered that based on the clinical data presented in the resubmission, the claim of superior comparative effectiveness of T-DXd compared with T-DM1 was reasonable.
- 12.15 The resubmission noted the PBAC's recommendation from July 2022, that the claim of non-inferior comparative safety of T-DXd compared with T-DM1 was not adequately supported by the data and that T-DXd has a worse but manageable safety profile. However, the resubmission did not revise the initial non-inferior clinical claim for safety and emphasised that all observed adverse events are known and manageable. The PBAC reiterated their original finding of inferior but manageable safety for T-DXd.

Economic analysis

- 12.16 As an early resolution resubmission, the economic analysis has not been independently evaluated.
- 12.17 At the July 2022 meeting, the PBAC stated that the changes shown in Table 21 may address the outstanding economic issues without requiring further re-evaluation, consistent with an early resolution pathway (see paragraphs 7.8, 7.9, 7.10, 7.12). Table 21 shows how the resubmission addressed each of these issues. A number of additional changes were made to the economic model in the resubmission that were not requested by the PBAC and have not been evaluated; these changes are not presented in Table 21.

Table 21: Summary of changes made in the resubmission with respect to the economic analysis

PBAC PSD recommended change July 2022	Early resolution resubmission change December 2022	Addressed?
Address the overestimated extrapolated gain in PFS and OS		
Specify a data truncation point of 18 months for both T-DXd and T-DM1 arms.	The resubmission proposed that data should be truncated at the point where 20% of patients remain at risk of an event. PFS T-DXd: 30 months PFS T-DM1: 18 months OS T-DXd: 34 months OS T-DM1: 33 months.	No, although use of IA2 data may support extrapolation from a point beyond 18 months. The PBAC noted that the truncation point for PFS for T-DM1 was earlier than for T-DXd, and that further justification for this as well as the impact on the ICER was required given the duration of follow-up for both arms would be similar.
Use a log-logistic parametric function as the extrapolation for T-DXd PFS. Use an independently fitted gamma function for the T-DXd arm OS and an independently fitted Weibull function for the T-DM1 arm OS.	The resubmission updated the KM data for IA2 and retained the choice of parametric functions from the July 2022 submission: independent log-normal (for both T-DXd and T-DM1 arms) and dependent Weibull (for both T-DXd and T-DM1 arms), for PFS and OS, respectively.	No. The PBAC considered that without further evaluation of the model the parametric functions (with IA1 KM data) as recommended in July 2022 should be used: <u>PFS</u> T-DXd: independent log-logistic T-DM1: independent log-normal. <u>OS</u> T-DXd: independent gamma T-DM1: independent Weibull.
Amend the cost and likelihood of subsequent anti-cancer therapies		
Remove 6 months of subsequent anti-cancer therapy costs and disease management costs from the end-of-life care costs to avoid double counting.	The resubmission adopted the PBAC's advice from July 2022 and reduced the subsequent anti-cancer therapy costs from \$[REDACTED] to \$[REDACTED] per average patient.	Yes. The PBAC noted that the Sponsor accepted these recommendations for subsequent anti-cancer therapies in their PSCR and pre-PBAC response prior to the July 2022 meeting.
Increasing the proportion of patients in each arm with progressive disease who would receive subsequent anti-cancer therapies to 100% rather than a reduced fraction.	The resubmission adopted the PBAC's advice from July 2022 and adjusted the proportion to 100% for both T-DXd and T-DM1 arms.	
Normalise the cost of subsequent anti-cancer therapies to 100% per cycle for each patient who receives subsequent therapies so that patients cannot receive more than one anti-cancer therapy at a time.	The resubmission adopted the PBAC's advice from July 2022 and adjusted the proportion to 100% for both T-DXd and T-DM1 arms.	
Reduce the cost of T-DXd so that the resulting ICER is below \$75,000/QALY gained		
After making the above mentioned adjustments to the economic model, reduce the cost of T-DXd so that the resulting ICER is below \$75,000/QALY gained, consistent with treatments for mBC previously considered by PBAC.	The resubmission proposed that an ICER of \$[REDACTED]/QALY was acceptable using a revised model as it is in line with previous PBAC advice for therapies in this therapeutic area (tucatinib PSD, March 2021 PBAC meeting).	No. The PBAC re-iterated that an ICER below \$75,000/QALY is appropriate, using the model recommended by the PBAC in July 2022, incorporating IA2 PFS and OS data, and incorporating the T-DM1 RSA if relevant.

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

IA2 = Interim Analysis 2; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; PSD = Public Summary Document; QALY = Quality adjusted life year; RSA = risk sharing arrangements; T-DXd = trastuzumab deruxtecan; T-DM1 = trastuzumab emtansine.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

12.18 The results of the economic evaluation for the resubmission generated an ICER of \$75,000 to < \$95,000/QALY gained (ex-manufacturer [EMP] price \$¹), reduced from the ICER considered by the PBAC in July 2022 (\$115,000 to < \$135,000/QALY; EMP \$¹). The resubmission retained the parametric extrapolation functions used in the July 2022 submission rather than incorporating the PBAC's advice shown in Table 21. Table 22 summarises the model results for the two submissions.

Table 22: Model results from the July 2022 and December 2022 PBAC considerations

Model	Proposed ex-man price for T-DXd	ICER (cost/QALY)
July 2022 submission	\$ ¹	\$ ¹
July 2022 PBAC	\$ ¹	\$ ²
July 2022 PBAC model scenario with reduced price	\$ ¹	\$ ¹
December 2022 resubmission ^a	\$ ¹	\$ ³
July 2022 PBAC model scenario ^b with reduced price and the IA2 PFS and OS data, and the associated updated data truncation points from the December 2022 resubmission	\$ ¹	\$ ³

IA2 = Interim Analysis 2; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = Quality adjusted life year; T-DXd = trastuzumab deruxtecan; T-DM1 = trastuzumab emtansine.

^a Consistent with an early resolution resubmission, the December 2022 resubmission model was not evaluated.

^b This scenario included PBAC-preferred extrapolation functions (based on IA2) for PFS: T-DXd: independent log-logistic, T-DM1: independent log-normal; and OS: T-DXd: independent gamma; T-DM1: independent Weibull.

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$155,000 to < \$255,000

³ \$75,000 to < \$95,000

12.19 The PBAC considered that the evaluated model from the July 2022 consideration, with the changes recommended in Section 7 of the PSD, should be retained as the re-specified base case model. Justifications for the PBAC's approach can be found in paragraphs 6.21 to 6.43 of the July 2022 PSD. The ICER in the resubmission using the unevaluated model was \$75,000 to < \$95,000/QALY gained, which was substantially less than the ICER of \$115,000 to < \$135,000/QALY gained using the PBAC scenario from the July 2022 meeting and the revised price. The PBAC noted that if IA2 PFS and OS data are added to July 2022 model with the associated updated data truncation points from the December 2022 resubmission, the ICER reduces to \$75,000 to < \$95,000/QALY gained, which remains higher than the \$75,000 to < \$95,000/QALY gained presumably due to the additional changes made by the Sponsor in the updated December 2022 model. However, the PBAC noted that as an early resolution resubmission, the additional changes could not be evaluated and therefore were not considered or accepted by the PBAC.

- 12.20 The PBAC noted there is no Special Pricing Arrangement (SPA) for T-DM1 and therefore the effective price for T-DM1 is the same as its published price. However, the PBAC noted that if the average price of T-DM1 is managed through an RSA,¹⁰ the agreed cost-effective price for T-DM1 should be incorporated into the economic model for T-DXd.

Estimated PBS usage & financial implications

- 12.21 As an early resolution resubmission, the estimated utilisation and financial implications have not been independently evaluated.
- 12.22 At the July 2022 meeting, the PBAC stated that a revision to the financial estimates to (i) include a lower T-DXd cost as per the revised economic evaluation; and (ii) amend the eligible patient population, may address the outstanding financial issues without requiring further re-evaluation, consistent with an early resolution pathway (see paragraphs 7.11 and 7.12). The PBAC noted that the eligible patient population should comprise:
- an incident pool of patients eligible for treatment with T-DXd in the second-line setting aligning with the number of patients currently initiating T-DM1 therapy;
 - a small pool of patients who relapse during or within 6 months of adjuvant HER2 directed treatment;
 - a prevalent pool of patients currently receiving second-line T-DM1, assuming 85% of patients are expected to progress to third-line T-DXd during the first and second year of treatment;
 - a small prevalent pool of patients receiving third-line and later-line therapies, who are expected to progress during the first year of treatment.
- 12.23 Table 23 shows a summary of changes made in the resubmission. Additional changes were made to the financial impact in the resubmission that were not requested by the PBAC and have not been evaluated.

¹⁰ [Pharmaceutical Benefits Scheme \(PBS\) | TRASTUZUMAB EMTANSINE, injections, 100 mg vial and 160 mg vial, Kadcyla®, Roche Products Pty Ltd.](#)

[Pharmaceutical Benefits Scheme \(PBS\) | Medicines for HER2 positive metastatic breast cancer, February 2018.](#)

Table 23: Summary of changes made in the resubmission with respect to the financial analysis

PBAC PSD recommended change July 2022	Early resolution resubmission change December 2022	Addressed?
Epidemiological variables		
An incident pool of patients eligible for treatment with T-DXd in the 2L setting aligning with the number of patients currently initiating T-DM1 therapy (2L initiations). [Paragraph 7.11 July 2022 PSD]	The resubmission provided estimates for continuing patients for pertuzumab in each year of the analysis, and assumed that all patients discontinuing treatment would be eligible for treatment in 2L. The resubmission stated that the updated approach was informed by incident and prevalent patient data for pertuzumab from DoH.	No. The resubmission based estimates on patients discontinuing pertuzumab rather than the advice from the PBAC which was to use the number of patients initiating 2L T-DM1.
A small pool of patients who relapse during or within 6 months of adjuvant HER2 directed treatment (rapid relapse patients). [Paragraph 7.11 July 2022 PSD]	The resubmission stated that this was informed by incident patient data for T-DM1 from DoH, and assumed that 8% of patient's incident patients will experience rapid relapse.	No. The PBAC considered the number of early relapse patients to be over-estimated due to assuming exponential growth whereas the data indicate the utilisation of T-DM1 for early breast cancer has stabilised.
A prevalent pool of patients currently receiving 2L T-DM1, assuming 85% of patients are expected to progress to 3L T-DXd during the first and second year of treatment (3L initiations). [Paragraph 7.11 July 2022 PSD]	The resubmission stated that prevalent T-DM1 patients initiating treatment with T-DXd in the 3L were informed by data from DoH. It was estimated in 2023 that there would be [REDACTED] ¹ prevalent patients treated with T-DM1 and of these [REDACTED] ¹ (85%) would receive T-DXd.	Appears consistent with recommended approach.
A small prevalent pool of patients receiving 3L and later-line therapies, who are expected to progress during the first year of treatment (3L plus initiations). [Paragraph 7.11 July 2022 PSD]	The resubmission stated that the estimates are informed by prevalence data from DoH for patients receiving trastuzumab monotherapy in 2L+, and assumed that 70% of this prevalent pool will switch to T-DXd the first year of listing. It was estimated in 2023 that there would be [REDACTED] ¹ prevalent patients and of these [REDACTED] ¹ (70%) would receive T-DXd. This compares with [REDACTED] ² patients in Year 1 in the July 2022 submission.	No. The PBAC expected this to be a small pool of patients based on the July 2022 submission, although acknowledged that further data was available to inform the revised estimates. The resubmission included 2L+ trastuzumab patients rather than 3L+.
Grandfather patients	The resubmission estimated that a bolus of [REDACTED] patients from the T-DXd access program will require grandfathering on the PBS in the first year of listing.	This change was not requested by PBAC in July 2022.
Other estimates		
Reduction in the T-DXd proposed price [Paragraph 7.12 July 2022 PSD]	\$[REDACTED] per 100 mg vial, compared to \$[REDACTED] per 100 mg vial in the July 2022 submission (EMP prices).	No. The price reduction did not achieve an ICER of below \$75,000/QALY using the July 2022 model.
Treatment duration	DTG method applying average duration of treatment for T-DXd informed by extrapolation of TTD Kaplan-Meier curve using Generalised Gamma function from the economic model.	No. This change was not requested by PBAC in July 2022. A shorter mean treatment duration

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

PBAC PSD recommended change July 2022	Early resolution resubmission change December 2022	Addressed?
		was assumed for patients initiating treatment in the 3L+ setting (19.1 versus 29.01 months).

Source: Adapted from resubmission Table 4.1-1.

DoH = Department of Health; DTG = duration of treatment group; EMP = ex-manufacturer price; HER2 = human epidermal growth factor receptor 2; 2L = second line; 3L = third line; N/A = not applicable; PSD = Public Summary Document; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TTD = time to treatment discontinuation.

The redacted values correspond to the following ranges:

¹500 to < 5,000

²< 500

12.24 The financial implications of listing T-DXd according to the December 2022 resubmission are presented in Table 24. The estimates from the July 2022 submission are shown underneath.

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

Table 24: Estimated use and financial implications (based on proposed effective price of T-DXd)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
December 2022 resubmission						
Estimated extent of use						
2L incident patients: based on those discontinuing pertuzumab	1	1	1	1	1	1
1L incident patients: 8% of T-DM1 eBC patients	1	1	1	1	1	1
2L prevalent patients: 85% of T-DM1 prevalent patients	1	1	1	1	1	1
3L+ prevalent patients: 70% of 2L trastuzumab monotherapy patients	2	1	1	1	1	1
Grandfather patients	1	-	-	-	-	-
Total number of patients initiating T-DXd	2	2	1	1	1	1
Number of scripts dispensed ^a	3	4	5	6	6	6
Estimated financial implications of T-DXd						
Cost to PBS/RPBS less copayments	\$ 7	\$ 8	\$ 7	\$ 9	\$ 10	\$ 10
Estimated financial implications for T-DM1, trastuzumab sub-cutaneous, lapatinib and capecitabine						
Cost to PBS/RPBS less copayments ^b	11	11	11	11	11	11
Net financial implications						
Net cost to PBS/RPBS	\$ 7	\$ 8	\$ 7	\$ 9	\$ 10	\$ 10
Net cost to MBS	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11
July 2022 submission						
Estimated extent of use						
Number of scripts dispensed ^a	6	6	5	5	5	3
Estimated financial implications of T-DXd						
Cost to PBS/RPBS less copayments	\$ 7	\$ 7	\$ 7	\$ 8	\$ 8	\$ 8
Estimated financial implications for T-DM1, trastuzumab sub-cutaneous, lapatinib and capecitabine						
Cost to PBS/RPBS less copayments	\$ 12	\$ 13	\$ 14	\$ 14	\$ 14	\$ 15
Net financial implications						
Net cost to PBS/RPBS	\$ 10	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7
Net cost to MBS	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11

Source: Table 4.3-2 p65, Table 4.3-3 p65, Table 4.3-5 p66, Table 4.5-2 p67 of the December 2022 resubmission.

Table 4.14 p175, Table 4.15 p175, Table 4.17 p176, Table 4.24 p179, Table 4.27 p181 of the July 2022 submission.

MBS = Medicare Benefits Schedule; (R)PBS = (Repatriation) Pharmaceutical Benefits Scheme; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

^a Scripts are estimated based on duration of treatment. Patients who continue treatment into a subsequent year contribute to scripts in that subsequent year.

^b The financial estimates in the resubmission removed all cost offsets for existing 2L therapies that were included in the July 2022 submission.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 30,000 to < 40,000

⁴ 40,000 to < 50,000

⁵20,000 to < 30,000

⁶10,000 to < 20,000

⁷\$100 million to < \$200 million

⁸\$200 million to < \$300 million

⁹\$90 million to < \$100 million

¹⁰\$80 million to < \$90 million

¹¹\$0 to < \$10 million

¹²\$20 million to < \$30 million

¹³\$30 million to < \$40 million

¹⁴\$40 million to < \$50 million

¹⁵\$50 million to < \$60 million

- 12.25 According to the resubmission, the estimated financial impact over the first 6 years of listing is \$700 million to < \$800 million (EMP = \$| per vial), compared with \$800 million to < \$900 million (EMP = \$| per vial) according to the July 2022 submission.
- 12.26 The PBAC noted the financial estimates in the resubmission were based on materially different assumptions compared with the July 2022 submission. For example, compared to the July 2022 submission, the resubmission had significantly more treated patients in Year 1 (500 to < 5,000 vs 500 to < 5,000). Overall, the total prescriptions in the resubmission increased to 100,000 to < 200,000 over Years 1-6, compared with 100,000 to < 200,000 in the July 2022 submission, an increase of 7%.
- 12.27 The resubmission removed all cost offsets that were included in the first submission, stating that listing of T-DXd will displace these therapies from 2L to 3L (paragraph 6.58).

Financial Management – Risk Sharing Arrangements

- 12.28 In anticipation of the need for a Risk Share Arrangement (RSA), the resubmission requested a Deed of Agreement that is exclusive to T-DXd in HER2+ mBC.
- 12.29 The resubmission stated that given the significant uncertainty in rate of uptake of T-DXd in prevalent mBC populations, it proposed |||| for the period of the Deed of Agreement, whereby ||||| from Year 1 ||||| for Year 1, and so on.

For more detail on PBAC's view, see section 13 PBAC outcome.

13 PBAC Outcome

- 13.1 The PBAC deferred making a recommendation for trastuzumab deruxtecan (T-DXd) for the treatment of human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer (mBC) for patients who have progressed following a prior HER2 directed therapy for metastatic disease, or relapsed during or within 6 months of receiving adjuvant HER2 directed therapy, to allow further consultation with the sponsor regarding a cost-effective price for T-DXd and the financial estimates. In deciding to defer making a recommendation, the PBAC noted a further price reduction would be required to meet the cost-effectiveness parameters outlined at the July 2022 meeting. The PBAC also noted the estimates of use in the resubmission appeared overestimated.

- 13.2 The PBAC noted its consideration of the resubmission under the early resolution pathway was hindered by the inclusion of a number of changes to the economic model and financial forecasts that were outside of the specified changes for this pathway. The PBAC advised that consideration of any additional information provided by the sponsor under the early resolution pathway should be contingent on it being consistent with that requested at the July 2022 meeting (paragraph 7.12) and it being easily reconcilable with the information independently evaluated as part of the July 2022 submission such that further evaluation is not required.
- 13.3 The PBAC noted a consumer comment (further to those received in July 2022) highlighting that a delay in recommending subsidy for T-DXd was a burden for patients in terms of a requirement for private funding, reduced equity of access and prolonged psychosocial distress.
- 13.4 The PBAC considered that the restriction proposed by the resubmission was unnecessarily complex given the low risk of use outside the restriction in the HER2 low patient population, and that the restriction should revert to that described in the July 2022 PSD. The PBAC commented that changes to the patient population described in the restriction were not requested by the PBAC in July 2022 and were not appropriate. The PBAC noted the resubmission's request for the initial script for T-DXd to be a written authority to ameliorate the risk of use outside the restriction. However, the PBAC maintained its advice from July 2022 that a written authority would not be required and that a telephone/online PBS authority for T-DXd would be appropriately in line with the restriction type for T-DM1.
- 13.5 The PBAC acknowledged that the Interim Analysis 2 (IA2) of the DB03 trial provided greater certainty in the longer-term outcomes for T-DXd. The PBAC noted an improvement in PFS (HR=0.33), an improvement in OS (HR=0.64), and a worse but manageable safety profile (events of concern in the trial were nausea, diarrhoea, interstitial lung disease).
- 13.6 The PBAC noted that a subgroup analysis of the DB03 trial by age (<65 vs ≥65 years) indicated a reduced benefit for OS in patients ≥65 years for T-DXd over T-DM1, with a point estimate unfavourable to T-DXd (HR=1.29), in contrast with patients <65 years (HR=0.54). The PBAC noted from DUSC advice that 33% of T-DM1 initiations over the period 2015-21 were in the ≥65 years age group, and therefore the benefit of T-DXd in the Australian population may be less than that observed in the DB03 trial, where the median age was 54 years and only 19% of patients were older than 65 years.
- 13.7 The PBAC considered that the evaluated model from the July 2022 consideration should be retained as the basis for the re-specified base case model. The PBAC noted the economic model presented in the resubmission could not be reconciled with the July 2022 evaluated model due to the large number of changes made. The PBAC requested that the sponsor provide the July 2022 evaluated model for the PBAC

scenario as outlined in paragraph 7.10 (ICER of \$155,000 to < \$255,000/QALY gained) with the following changes highlighted and provided in a stepwise manner:

- Reduced price for T-DXd;
 - Inclusion of PFS and OS data from IA2 of the DB03 trial using the extrapolation functions recommended by the PBAC in July 2022. The PBAC noted it would be appropriate to revise the time point from which the extrapolations are applied, however also noted the time point at which PFS was extrapolated for T-DM1 in the resubmission appeared inconsistent with that for T-DXd; and
 - Inclusion of time to treatment discontinuation (TTD) from IA2 of the DB03 trial using the same extrapolation functions as for the July 2022 model.
- 13.8 The PBAC noted that the average price of T-DM1, as managed through an RSA, would need to be applied in the economic model for T-DXd. As the details of such arrangements are confidential, the sponsor will not be able to calculate the required price to accommodate the T-DM1 RSA prior to a positive recommendation for T-DXd.
- 13.9 The PBAC noted that if the reduced price for T-DXd and the IA2 PFS and OS data with the associated updated data truncation points from the December 2022 resubmission are added to July 2022 model, the ICER is \$75,000 to < \$95,000/QALY gained. The PBAC reaffirmed its July 2022 advice that an ICER below \$75,000/QALY gained is appropriate and therefore noted that the price needs to be further reduced.
- 13.10 The PBAC recalled the patient population for T-DXd comprises the following four groups:
- an incident pool of patients eligible for treatment with T-DXd in the second-line setting aligning with the number of patients currently initiating T-DM1 therapy. The PBAC noted the resubmission estimated this pool of patients based on patients discontinuing treatment with pertuzumab. The PBAC noted the standard approach would be to use the number of patients initiating T-DM1;
 - a small pool of patients who relapse during or within 6 months of adjuvant HER2 directed treatment. The PBAC noted that it was assumed that 8% of patients treated with T-DM1 for early breast cancer were assumed to have a rapid relapse. The PBAC noted the exponential growth applied to forecast future use appeared to over-estimate patients as the data for more recent months indicate the utilisation of T-DM1 for early breast cancer has stabilised;
 - a prevalent pool of patients currently receiving second-line T-DM1, assuming 85% of patients are expected to progress to third-line T-DXd during the first and second year of treatment;
 - a small prevalent pool of patients receiving third-line and later-line therapies, who are expected to progress during the first year of treatment. The PBAC noted that the resubmission estimated this pool of patients based on those receiving

14 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

15 Sponsor's Comment

The sponsor had no comment.

Addendum to the December 2022 Public Summary Document:

**14.08 TRASTUZUMAB DERUXTECAN,
Powder for I.V. infusion 100 mg,
Enhertu[®],
AstraZeneca Pty Ltd.**

16 Background

- 16.1 The resubmission requested a Section 100, Authority Required listing for trastuzumab deruxtecan (T-DXd; Enhertu[®]) for the treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer (BC) in patients who have progressed following a prior HER2 directed therapy for metastatic disease, or relapsed during or within 6 months of receiving a HER2 directed adjuvant therapy.
- 16.2 At the December 2022 PBAC meeting, the PBAC deferred their decision regarding the requested listing of T-DXd. The resubmission provided further information following the deferral and sought to address the PBAC's concerns from its December 2022 meeting. The PBAC considered that the following changes may address the outstanding issues without requiring re-evaluation:
- The requested restriction should revert to that described in the July 2022 Public Summary Document (PSD), as the restriction proposed by the December 2022 resubmission was unnecessarily complex (paragraph 13.4).
 - The economic model should be amended with respect to extrapolation functions and the time point from which they are applied, and include time to treatment discontinuation (TTD) (paragraph 13.7);
 - The price of T-DXd should be reduced so that the resulting incremental cost effectiveness ratio (ICER) is below \$75,000 per quality adjusted life year (QALY) gained (paragraph 13.9); and
 - The financial estimates should be adjusted to include a lower T-DXd price, revised eligible patient population, and cost offsets for therapies that will be replaced by T-DXd (paragraphs 13.10 to 13.13).
- 16.3 Table 25 summarises how the resubmission addressed each of these issues.

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

Table 25: Summary of changes made in the resubmission

PBAC PSD recommended change July 2022 and/or December 2022	Resubmission change March 2023	Addressed?
Requested listing		
The requested restriction should revert to that described in the July 2022 PSD (paragraph 13.4), describing 2 groups of patients.	The resubmission maintained the request from December 2022 for 5 groups of patients over 3 restrictions with some temporary criteria.	No. Aside from grandfathering, the PBAC considered temporary restrictions are not practical for prescribers and patients. The requested restriction is unnecessarily complex and requires simplification.
Economic model		
The evaluated model from the July 2022 consideration should be retained as the basis for the re-specified base case model. The economic model should be amended (paragraphs 13.7 and 13.9, and Table 21).	The resubmission used the PBAC preferred parametric functions in the updated model.	Yes, although the average price of T-DM1, as managed through a confidential RSA, would need to be applied in the economic model for T-DXd.
Financial estimates		
The financial estimates should be adjusted to include a lower T-DXd price, revised eligible patient population, and cost offsets for therapies that will be replaced by T-DXd (paragraphs 13.10 to 13.13).	The resubmission provided updated patient numbers and financial estimates based on the PBAC's advice, with the exception of advice related to trastuzumab monotherapy prevalent patients and reduction in the number of prescriptions for PBS patients.	Yes, although there is no reliable patient estimate for later line patients on trastuzumab monotherapy who would be fit enough for T-DXd and their mean time-on-treatment.
Risk sharing arrangements		
The PBAC indicated that a cap for T-DXd that is separate to that for T-DM1 may be required, but noted that [REDACTED] would not be acceptable given the assumed large pool of prevalent patients for which the cost-effectiveness is unknown (paragraphs 13.10 and 13.15).	The resubmission proposed the four elements for an RSA to manage the risk of use in patients switching from prevalent populations to T-DXd, in the absence of rolling caps.	No. The underpinning financial estimates require revision with respect to trastuzumab monotherapy prevalent patients.

PSD = Public Summary Document; RSA = risk sharing arrangement; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

17 Requested listing

17.1 The requested restriction remained unchanged from that requested at the December 2022 intracycle meeting. The elements of that restriction were:

- Defining 5 patient groups over 3 restrictions;
- Requesting the initial script for T-DXd to be a written authority to ameliorate the risk of use outside the restriction.

17.2 Table 26 summarises the changes made to the requested listing in the resubmission.

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

Table 26: Summary of changes made in the resubmission with respect to the requested listing

PBAC PSD recommended change July 2022 and/or December 2022	Resubmission change March 2023	Addressed?
The requested restriction should revert to that described in the July 2022 PSD (paragraph 13.4), describing 2 groups of patients:	The resubmission maintained the request from December 2022 for 5 groups of patients over 3 restrictions with some temporary criteria:	No. Aside from grandfathering, the PBAC considered temporary restrictions are not practical for prescribers and patients. The requested restriction is unnecessarily complex and requires simplification.
Group 1: The condition must have progressed during or within 6 months following adjuvant treatment with a HER2 directed therapy.	Group 1: The condition must have progressed during or within 6 months following adjuvant treatment with a HER2 directed therapy as the most recent therapy (Restriction 1).	
Group 2: The condition must have progressed following treatment with at least one prior HER2 directed regimens for metastatic breast cancer.	Group 2: The condition must have progressed following treatment with pertuzumab and trastuzumab in combination as the most recent therapy in the metastatic setting (Restriction 1).	
	Group 3: The condition must have progressed following treatment with T-DM1 as the most recent therapy in the metastatic setting (Restriction 1; access removed after 2 years).	
	Group 4: Patient must have progressed following treatment with at least two prior HER2 directed therapies in the metastatic setting AND the most recent treatment (during which the condition progressed) was trastuzumab (Restriction 2; access removed after 1 year).	
	Group 5: Grandfathered patients from the AZ access program (Restriction 3; access removed after 1 year).	
A telephone/online PBS authority level for T-DXd would be appropriately in line with the restriction type for T-DM1.	The resubmission maintained the request for a written authority level.	No. The PBAC considered written authority level for initial therapy with T-DXd is not required.

HER2 = human epidermal growth factor receptor 2; PSD = Public Summary Document; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

- 17.3 In July 2022, the PBAC considered that the requested written authority level for initial therapy with T-DXd was not required and that a telephone/online PBS authority level for T-DXd with 3 repeats would be appropriately in line with the restriction type for T-DM1. At the December 2022 and March 2023 considerations, the PBAC maintained this position.
- 17.4 The resubmission maintained from the December 2022 consideration that the definition of 5 patient groups over 3 restrictions with some temporary criteria were necessary to mitigate the risk of a delay in switch to T-DXd from the prevalent T-DM1 and trastuzumab populations. The resubmission stated that unrestricted uptake in these significant combined populations would create untenable risk if incorporated in a risk sharing arrangement (RSA) that included annual expenditure caps.

- 17.5 The resubmission maintained from the December 2022 consideration that initiations to T-DXd from (1) prevalent T-DM1 patients and (2) prevalent trastuzumab patients should be limited to the first 2 years and 1 year after T-DXd listing, respectively, to minimise the risk of any use in these populations after these periods of time.

For more detail on PBAC's view, see section 19 PBAC outcome.

18 Consideration of the evidence

Economic analysis

- 18.1 As a resubmission to provide further information addressing the previous deferral, the economic analysis has not been independently evaluated.
- 18.2 At the December 2022 meeting, the PBAC stated that the changes shown in Table 27 may address the outstanding economic issues without requiring further evaluation (see paragraph 13.7). Table 27 shows how the resubmission addressed each of these issues.

Table 27: Summary of changes made in the resubmission with respect to the economic analysis

PBAC PSD recommended change July 2022 and/or December 2022	Resubmission change March 2023	Addressed?
The evaluated model from the July 2022 consideration should be retained as the basis for the re-specified base case model. The economic model should be amended as follows (paragraphs 13.7 and 13.9, and Table 21):	The resubmission used the PBAC preferred parametric functions in the updated model:	

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

PBAC PSD recommended change July 2022 and/or December 2022	Resubmission change March 2023	Addressed?
• Include PFS and OS data from IA2 of the DB03 trial using the extrapolation functions recommended by the PBAC in July 2022.	• Extrapolation functions: ▪ PFS: T-DXd = log-logistic independent; ▪ T-DM1 = log-normal independent; ▪ OS: T-DXd = gamma independent; ▪ TDM1 = Weibull independent.	Yes.
• Use consistent time points for T-DXd and T-DM1 to apply the extrapolation using IA2 data, noting that IA2 data may support extrapolation from a point beyond 18 months.	• The resubmission retained the truncation points from the December 2022 resubmission, i.e. proposing that data should be truncated at the point where 20% of patients remain at risk of an event. ▪ PFS T-DXd: 30 months ▪ PFS T-DM1: 18 months ▪ OS T-DXd: 34 months ▪ OS T-DM1: 33 months.	Yes.
• Include the additional changes from the July 2022 model (as addressed in the December 2022 model) regarding the cost and likelihood of subsequent anti-cancer therapies.	• The additional changes addressed in the December 2022 model were carried through to the March 2023 model.	Yes.
• Reduce the cost of T-DXd so that the resulting ICER is below \$75,000/QALY gained.	The resubmission proposed an effective AEMP of \$[REDACTED] per vial, reduced from \$[REDACTED] in the December 2022 submission ([REDACTED] % reduction) and \$[REDACTED] in the July 2022 submission ([REDACTED] % reduction). The model changes and price reduction drove a decrease in the ICER from \$[REDACTED]¹ (July 2022) and \$[REDACTED]² (December 2022) to \$[REDACTED]³/QALY gained.	Yes. However, the average price of T-DM1, as managed through a confidential RSA, would need to be applied in the economic model for T-DXd.

DB03 = DESTINY-Breast 03; IA2 = Interim Analysis 2; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; RSA = risk sharing arrangement; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TTD = time to treatment discontinuation.

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$75,000 to < \$95,000

³ \$55,000 to < \$75,000

18.3 The results of the economic evaluation for the resubmission generated an ICER of \$55,000 to < \$75,000/QALY gained (ex-manufacturer [EMP] price \$[REDACTED]). Table 28 summarises the model results for the submissions.

Table 28: Model results from the July 2022, December 2022 and March 2023 considerations

Model	Proposed ex-man price for T-DXd	ICER (cost/QALY)
July 2022 submission	\$ [REDACTED]	\$ [REDACTED] ¹
July 2022 PBAC model scenario	\$ [REDACTED]	\$ [REDACTED] ²
July 2022 PBAC model scenario with reduced price	\$ [REDACTED]	\$ [REDACTED] ¹
July 2022 PBAC model scenario with reduced price and the IA2 PFS and OS data, and the associated updated data truncation points from the December 2022 resubmission	\$ [REDACTED]	\$ [REDACTED] ³
March 2023 resubmission	\$ [REDACTED]	\$ [REDACTED] ⁴

IA2 = Interim Analysis 2; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = Quality adjusted life year; T-DXd = trastuzumab deruxtecan; T-DM1 = trastuzumab emtansine.

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$155,000 to < \$255,000

³ \$75,000 to < \$95,000

⁴ \$55,000 to < \$75,000

Estimated PBS usage & financial implications

- 18.4 As a resubmission to provide further information addressing the previous deferral, the estimated utilisation and financial implications have not been independently evaluated.
- 18.5 At the December 2022 meeting, the PBAC stated that the changes shown in Table 29 may address the outstanding financial issues without requiring further evaluation (see paragraphs 13.10 to 13.13). Table 29 shows how the resubmission addressed each of these issues.

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

Table 29: Summary of changes made in the resubmission with respect to the financial analysis

PBAC PSD recommended change July 2022 and/or December 2022	Resubmission change March 2023	Addressed?
The financial estimates should be adjusted to include a lower T-DXd price, revised eligible patient population, and cost offsets for therapies that will be replaced by T-DXd (paragraphs 13.10 to 13.13).	The resubmission provided updated patient numbers and financial estimates based on the PBAC's advice, with the exception of advice related to trastuzumab monotherapy prevalent patients and reduction in the number of prescriptions for PBS patients.:	
Reduce the estimate for patients who relapse during or within 6 months of adjuvant HER2 directed treatment to 8% of patients treated with T-DM1 for early breast cancer with no increase for future use, as the utilisation of T-DM1 for early breast cancer has stabilised.	The resubmission estimated the number of patients as 8% of patients treated with T-DM1 for early breast cancer and removed the exponential growth applied to forecast future use (corresponds with Group 1 in requested restriction).	Yes.
Revise the estimate for patients eligible for treatment with 2L T-DXd from the number of patients initiating T-DM1, rather than patients discontinuing treatment with pertuzumab.	The resubmission estimated the number of patients from T-DM1 initiations and assumed [REDACTED]¹ patients in 2020 (corresponds with Group 2 in requested restriction).	Yes.
Estimate the patients eligible for treatment with 3L T-DXd from the number of prevalent patients currently on treatment with 2L T-DM1 and 85% of patients progressing during the first 2 years of listing (no change from December 2022 submission).	The resubmission's estimate for the number of 3L T-DXd patients did not change from the December 2022 resubmission (corresponds with Group 3 in requested restriction).	Yes, although temporary access via the restriction for first 2 years is not practical for prescribers and patients (see requested listing above).
Reduce the estimate for patients eligible for treatment with 3L+ T-DXd from the number of prevalent patients receiving trastuzumab monotherapy.	The resubmission estimated the number of 3L+ T-DXd patients from prevalent patients currently on treatment with trastuzumab monotherapy with ECOG status 1-2, and a reduction of [REDACTED]% to ameliorate uncertainty (corresponds with Group 4 in requested restriction).	No. There is insufficient evidence of cost effectiveness for these patients and no reliable estimate of patient numbers.
Revise the estimate for patients moving from the T-DXd access program to PBS supply, noting these patients were not accounted for separately in the July 2022 submission and may already be accounted for in Groups 1-4 patient populations.	The resubmission included [REDACTED]¹ patients moving from the access program to PBS supply in Year 1 (corresponds with Group 5 in requested restriction). This was reduced from [REDACTED]¹ patients (50% reduction) in the December 2022 resubmission.	Yes.
Reduce the estimate for the number of prescriptions per patient to account for shorter duration of treatment and dose interruptions/reductions in PBS patients compared to trial patients.	The resubmission did not account for a reduction in the number of prescriptions per PBS patient.	No, although the PBAC noted the treatment duration was consistent with that applied in the economic model.
Include cost offsets for substituted therapies noting that there will be some replacement of therapies with T-DXd (as well as displacement from 2L to 3L).	The resubmission included the cost offsets for substituted therapies.	Yes.

2L = second line; 3L = third line; 3L+ = third or later line; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following range:

¹ <500

18.6 The financial implications of listing T-DXd according to the March 2023 resubmission are presented in Table 30. The estimates from the December 2022 and July 2022 submissions are shown underneath.

Table 30: Estimated use and financial implications (based on proposed effective price of T-DXd)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
March 2023 resubmission: EMP = \$ [REDACTED]; estimated cost over 6 years = \$ [REDACTED]¹						
Estimated extent of use						
2L T-DXd						
Incident patients: based on 100% of those initiating T-DM1 [restriction Gp2]	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²
1L T-DXd						
Incident patients: 8% of T-DM1 eBC patients (rapid relapsers) [restriction Gp1]	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²
3L T-DXd						
Prevalent patients: 85% of T-DM1 prevalent patients ^a [restriction Gp3]	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²
3L+ T-DXd						
Prevalent patients: 70% of trastuzumab monotherapy patients [restriction Gp4]	[REDACTED] ³	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²
Grandfather patients [restriction Gp5]	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²
Total number of patients initiating T-DXd	[REDACTED] ³	[REDACTED] ³	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²	[REDACTED] ²
Number of scripts dispensed ^b	[REDACTED] ⁴	[REDACTED] ⁵	[REDACTED] ⁴	[REDACTED] ⁶	[REDACTED] ⁶	[REDACTED] ⁶
Estimated financial implications of T-DXd						
Cost to PBS/RPBS less copayments (\$)	[REDACTED] ⁷	[REDACTED] ⁷	[REDACTED] ⁷	[REDACTED] ⁸	[REDACTED] ⁹	[REDACTED] ⁹
Estimated financial implications for T-DM1, trastuzumab sub-cutaneous, lapatinib, pertuzumab and capecitabine						
Cost to PBS/RPBS less copayments (\$)	[REDACTED] ¹⁰	[REDACTED] ¹⁰	[REDACTED] ¹⁰	[REDACTED] ¹⁰	[REDACTED] ¹⁰	[REDACTED] ¹⁰
Net financial implications						
Net cost to PBS/RPBS (\$)	[REDACTED] ⁹	[REDACTED] ⁷	[REDACTED] ⁸	[REDACTED] ¹¹	[REDACTED] ¹¹	[REDACTED] ¹¹
Net cost to MBS (\$)	[REDACTED] ¹²	[REDACTED] ¹²	[REDACTED] ¹²	[REDACTED] ¹²	[REDACTED] ¹²	[REDACTED] ¹²
Sensitivity analysis performed by the Secretariat: EMP = \$ [REDACTED]; estimated cost over 6 years = \$ [REDACTED]¹³						
Net cost to PBS/RPBS excluding G4 (3L+ therapy) (\$)	[REDACTED] ¹⁴	[REDACTED] ⁹	[REDACTED] ⁹	[REDACTED] ¹¹	[REDACTED] ¹¹	[REDACTED] ¹¹
December 2022 resubmission: EMP = \$ [REDACTED]; estimated cost over 6 years = \$ [REDACTED]^{15 c}						
Net cost to PBS/RPBS (\$)	[REDACTED] ⁷	[REDACTED] ¹⁶	[REDACTED] ⁷	[REDACTED] ¹⁷	[REDACTED] ⁸	[REDACTED] ⁸
July 2022 submission: EMP = \$ [REDACTED]; estimated cost over 6 years = \$ [REDACTED]¹⁸						
Net cost to PBS/RPBS (\$)	[REDACTED] ⁸	[REDACTED] ⁷	[REDACTED] ⁷	[REDACTED] ⁷	[REDACTED] ⁷	[REDACTED] ⁷

Source: Table 4.3-2 p65, Table 4.3-3 p65, Table 4.3-5 p66, Table 4.5-2 p67 of the December 2022 resubmission.

Table 4.14 p175, Table 4.15 p175, Table 4.17 p176, Table 4.24 p179, Table 4.27 p181 of the July 2022 submission.

EMP = ex-manufacturer price; MBS = Medicare Benefits Schedule; (R)PBS = (Repatriation) Pharmaceutical Benefits Scheme; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

^a Assumes that 60% and 40% of patients will elect treatment with T-DXd in Years 1 and 2, respectively.

*Public Summary Document – July 2022 PBAC Meeting with December 2022, March 2023
& July 2023 Addenda*

^b Scripts are estimated based on duration of treatment. Patients who continue treatment into a subsequent year contribute to scripts in that subsequent year.

^c The financial estimates in the December 2022 resubmission removed all cost offsets for existing 2L therapies that were included in the July 2022 submission.

The redacted values correspond to the following ranges:

¹ \$400 million to < \$500 million

² < 500

³ 5,000 to < 10,000

⁴ 20,000 to < 30,000

⁵ 40,000 to < 50,000

⁶ 10,000 to < 20,000

⁷ \$100 million to < \$200 million

⁸ \$80 million to < \$90 million

⁹ \$70 million to < \$80 million

¹⁰ net cost saving

¹¹ \$60 million to < \$70 million

¹² \$0 to < \$10 million

¹³ \$300 million to < \$400 million

¹⁴ \$40 million to < \$50 million

¹⁵ \$700 million to < \$800 million

¹⁶ \$200 million to < \$300 million

¹⁷ \$90 million to < \$100 million

¹⁸ \$800 million to < \$900 million

- 18.7 A sensitivity analysis (SA) was performed by the Secretariat, whereby the 3L+ trastuzumab monotherapy patients were excluded from the patient pool, reflecting the concern raised by the PBAC that T-DXd may not have the same level of efficacy and cost-effectiveness in these patients and the resubmission's proposed option to remove this group from the financial analysis. While these patients were only included in Year 1 of the financial estimates, the net cost reduces over 3 years compared to the March 2023 base case because the scripts from these patients are carried over to subsequent years. Without these patients, and accounting for cost offsets for substituted therapies in both the base case and SA, the total net forecast cost over 6 years is reduced from \$400 million to < \$500 million to \$300 million to < \$400 million.
- 18.8 The March 2023 resubmission's financial impact did not consider the number of prescriptions per patient being reduced due to PBS patients being older and more likely to have more co-morbidities and poorer performance status than patients in the trials, and having active/progressive brain metastases. The PBAC noted the treatment duration (and thus number of prescriptions) was consistent with that applied in the economic model, and in the earlier recommended treatment lines, the reductions in use would be expected to be less.
- 18.9 A summary of the percentage reductions in the T-DXd price and the net cost to the PBS/RPBS over 6 years, compared between the July 2022 and March 2023 considerations, is shown in Table 31.

Table 31: Summary of financial impact

	July 2022 ^a	March 2023 ^a	Percentage reduction from July 2022 to March 2023
T-DXd price (EMP)	\$█	\$█	%
Net cost to PBS/RPBS over 6 years	\$█ ¹	\$█ ²	%
Net cost to PBS/RPBS over 6 years with SA to exclude 3L+ patients	-	\$█ ³	%

EMP = ex-manufacturer price; SA = sensitivity analysis.

^a Both the July 2022 and March 2023 submissions included cost offsets for substituted therapies in the financial calculations.

The redacted values correspond to the following ranges:

¹ \$800 million to < \$900 million

² \$400 million to < \$500 million

³ \$300 million to < \$400 million

18.10 The PBAC noted that the estimates above do not account for the confidential treatment cycle cap for T-DM1 and the flow-on implications for T-DXd.

Financial Management – Risk Sharing Arrangements

18.11 The resubmission outlined changes to the proposed RSA, summarised in Table 32.

Table 32: Summary of changes made in the resubmission with respect to risk sharing arrangements

PBAC PSD recommended change July 2022 and/or December 2022	Resubmission change March 2023	Addressed?
The PBAC indicated that a cap for T-DXd that is separate to that for T-DM1 may be required, but noted that █ would not be acceptable given the assumed large pool of prevalent patients for which the cost-effectiveness is unknown (paragraphs 13.10 and 13.15).	The resubmission proposed the following elements for an RSA to manage the risk of use in patients switching from prevalent populations to T-DXd, in the absence of █: - Allow the temporary restriction criteria for patient groups (i) T-DM1 prevalent patients, and (ii) trastuzumab monotherapy prevalent patients, to ensure all switches from T-DM1 and trastuzumab monotherapy to T-DXd occur in the first 2 and 1 years, respectively. - Decrease by █% the number of patients who would receive T-DXd in the trastuzumab monotherapy prevalent patient pool in the annual caps in Year 1 of PBS listing, reducing this number from █¹ patients to █¹ patients. - Request RSA rebate to be less than 100%. - Request deed clause to allow █.	No. The underpinning financial estimates require revision with respect to 3L+ trastuzumab monotherapy prevalent patients.

3L+ = third or later line; RSA = risk sharing arrangement; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

For more detail on PBAC's view, see section 19 PBAC outcome.

19 PBAC outcome

19.1 The PBAC recommended the listing of trastuzumab deruxtecan (T-DXd) for the treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer for patients who have progressed following up to two prior lines of HER2 directed

therapy for metastatic disease, or relapsed during or within 6 months of receiving HER2 directed adjuvant therapy. The PBAC noted that the that Authority Required (telephone/online) listing should be available under the Section 100 (Efficient Funding of Chemotherapy) schedule. The PBAC is satisfied that T-DXd provides, for some patients, a substantial clinical benefit over trastuzumab emtansine (T-DM1) that is likely to translate into clinically meaningful gains in overall survival, and that T-DXd offers high added therapeutic value compared to the treatment options currently available. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost effectiveness of T-DXd would be acceptable using the economic model and price proposal in the March 2023 resubmission, with an adjustment to incorporate the cost effective price of trastuzumab emtansine as managed through a risk sharing arrangement (RSA). The PBAC considered that a RSA would be necessary for T-DXd to address uncertainty associated with the proposed PBS population including the potential for use in a broader patient population where the use may not be cost-effective. The PBAC considered it would be clinically appropriate for T-DXd to be used in a third and later line setting however, deferred its decision regarding the inclusion of these patients in its recommendation to seek further information on the likely size of this population and appropriate RSA parameters.

- 19.2 The PBAC noted that consistent with previous considerations, a telephone/online PBS authority level for T-DXd initial therapy would be appropriately in line with the restriction type for T-DM1. The PBAC considered that temporary restrictions are not practical for prescribers and patients and that the requested 5 patient groups over 3 restrictions would result in an overly complex listing. Further, applying 1 or 2 year time limits may disadvantage patients being well maintained on current therapy. The PBAC considered that T-DXd should be available for patients who have received up to 2 prior lines of HER2 directed therapy for metastatic disease, or patients who have relapsed during or within 6 months of receiving a HER2 directed adjuvant therapy. The PBAC noted that this can be defined in a single treatment phase listing. The PBAC also considered that the restriction should specify WHO performance of 0 or 1.
- 19.3 There was no clinical update for the March 2023 consideration but, consistent with their December 2022 consideration, the PBAC noted the improvements in PFS and OS using the Interim Analysis 2 (IA2) of the DB03 trial supported an interpretation of superior effectiveness and inferior but manageable safety of T-DXd compared to T-DM1.
- 19.4 The PBAC recalled that the evaluated economic model from the July 2022 consideration with the changes recommended in Section 7 of the July 2022 PSD should be retained as the re-specified base case model, using the IA2 PFS and OS data with the associated updated data truncation points from the December 2022 resubmission. The PBAC noted that the March 2023 resubmission used the PBAC preferred specifications in the updated model. The PBAC also recalled that an ICER below

\$75,000/QALY gained would be consistent with previous recommendations for treatments for metastatic breast cancer (paragraph 7.10), and noted that the resubmission model achieved an ICER of \$55,000 to < \$75,000/QALY gained when a █% price reduction compared to the December 2022 price was applied.

- 19.5 The PBAC recalled there is no SPA for T-DM1 and therefore the effective price for T-DM1 is the same as its published price. However, the PBAC noted that if the average price of T-DM1 is managed through an RSA,¹¹ the agreed cost-effective price for T-DM1 should be incorporated into the economic model for T-DXd and a price reduction would be required for T-DXd to be considered cost-effective.
- 19.6 The PBAC noted that for the population having received up to 2 prior lines of HER2 directed therapy, the resubmission largely addressed its concerns raised at the December 2022 consideration in terms of revising the eligible patient population and including cost offsets for replaced therapies. A sensitivity analysis that excluded the potential 3L+ T-DXd patients resulted in a decrease in estimated financial impact from \$400 million to < \$500 million to \$300 million to < \$400 million over the first 6 years of listing (not accounting for the required price reduction in T-DXd in the context of a T-DM1 RSA). The PBAC considered that the latter figure was a reasonable estimate of the financial impact for patients with up to two prior lines of HER2 directed therapy in the metastatic setting and patients who have relapsed during or within 6 months of receiving a HER2 directed therapy in the adjuvant setting. The PBAC noted that these estimates did not include a reduction in T-DXd treatment duration, but that the treatment duration was consistent with that applied in the economic model and was therefore acceptable. The PBAC noted the financial impact would be further decreased with the price reduction required to achieve cost-effectiveness.
- 19.7 The PBAC considered that uncertainties in the financial estimates and the potential for use in a broader patient population where the use may not be cost-effective should be managed by a RSA. The PBAC noted the March 2023 resubmission's request for: (i) temporary restrictions, (ii) a rebate of less than █%, and (iii) reduction of trastuzumab prevalent monotherapy patients. However, as discussed in relation to the recommended restriction and estimated utilisation (paragraphs 19.2 and 19.6), the PBAC considered that temporary restrictions were not acceptable and a financial cap for the current recommendation should exclude the prevalent group of trastuzumab monotherapy patients who have received at least 3 prior lines of HER2 therapy. The PBAC considered that as there are reliable patient estimates for the proposed T-DXd eligible population based on T-DM1 patient numbers and given the

¹¹ [Pharmaceutical Benefits Scheme \(PBS\) | TRASTUZUMAB EMTANSINE, injections, 100 mg vial and 160 mg vial, Kadcyla®, Roche Products Pty Ltd.](#)

[Pharmaceutical Benefits Scheme \(PBS\) | Medicines for HER2 positive metastatic breast cancer, February 2018.](#)

risk of leakage into the 3L+ population and the high financial impact of T-DXd, a 100% rebate would be appropriate for use exceeding the financial caps.

- 19.8 The PBAC considered it would be clinically appropriate for T-DXd to be used in a third and later line setting. However, the PBAC considered that there were residual issues associated with the estimate for the potential number of 3L+ T-DXd patients from prevalent patients currently on treatment with trastuzumab monotherapy. The PBAC considered the submission made unrealistic assumptions about the number of 3L+ line patients who would be fit enough to receive T-DXd and their mean time-on-treatment, and therefore the number of scripts in this group was overestimated. In the context of T-DXd effectiveness, cost effectiveness and size of this patient group being highly uncertain, the PBAC deferred its decision regarding the inclusion of these patients in its recommendation to seek further information on the likely size of this population and corresponding appropriate RSA parameters.
- 19.9 The PBAC recommended that T-DXd should not be treated as interchangeable with any other drugs.
- 19.10 The PBAC advised that T-DXd is not suitable for prescribing by nurse practitioners. The PBAC noted that existing HER2 directed therapies are not available for nurse prescribing.
- 19.11 The PBAC recommended that the Early Supply Rule should not apply to T-DXd. The PBAC noted that the Early Supply Rule does not apply to T-DM1.
- 19.12 The PBAC found that the criteria prescribed by the National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for T-DXd:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over the nominated comparator in terms of overall survival in the metastatic and adjuvant breast cancer populations;
 - b) The treatment is expected to address a high and urgent unmet clinical need as patients with HER2 positive breast cancer carry a heavy burden of disease despite the current medicines available;
 - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 19.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

20 Recommended listing

20.1 Add new medicinal product as follows:

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRASTUZUMAB DERUXTECAN Injection	NEW (Public) NEW (Private) MP	675 mg	8
Available brands			
Enhertu (trastuzumab deruxtecan 100 mg injection, 1 vial)			
Restriction Summary [new 1] / Treatment of Concept: [new 1.1]: Authority Required			
	Indication: Metastatic (Stage IV) HER2 positive breast cancer		
	Clinical criteria:		
	Patient must have evidence of human epidermal growth factor (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) in either the primary tumour/a metastatic lesion – establish this finding once only with the first PBS-prescription		
	AND		
	Clinical criteria:		
	The condition must have, at the time of treatment initiation with this drug, both: (i) progressed following prior HER2 directed therapy for metastatic breast cancer, (ii) been treated with at least one line of HER2 directed therapy, but not with more than two lines of drug therapy for metastatic disease; or		
	The condition must have, at the time of treatment initiation with this drug, progressed during/within 6 months following adjuvant treatment with a HER2 directed therapy		
	AND		
	Clinical criteria:		
	Patient must have/have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1.		
	AND		
	Clinical criteria:		
	The condition must be/have been untreated with this drug on the day of the first administered dose of this drug		
	AND		
	Clinical criteria:		
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.		
	AND		
	Clinical criteria:		
	The treatment must not be prescribed where any of the following is present: (i) left ventricular ejection fraction of less than 50%, (ii) symptomatic heart failure; cardiac function must be tested by either: (i) echocardiography (ECHO), (ii) multigated acquisition (MUGA); confirm cardiac function testing for the first PBS-prescription only		
	Treatment criteria:		
	Patient must be undergoing initial treatment with this drug – the following are true: (i) this is the first prescription for this drug, (ii) this prescription seeks no more than 3 repeat prescriptions; or		

	Patient must be undergoing continuing treatment with drug – the following are true: (i) there has been an absence of further disease progression whilst on active treatment with this drug, (ii) this prescription does not seek to re-treat after disease progression, (iii) this prescription seeks no more than 8 repeat prescriptions
	Prescribing Instructions: Confirm that the following information is documented/retained in the patient's medical records once only with the first PBS prescription: 1) Evidence of HER2 gene amplification (evidence obtained in relation to past PBS treatment is acceptable), 2) Details of prior HER2 directed drug regimens prescribed for the patient 3) Cardiac function test results (evidence obtained in relation to past PBS treatment is acceptable)
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
	Administrative Advice: Increased maximum amounts can be requested where a patient's weight is greater than 125 kg.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

21 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

22 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2023 Public Summary Document:

**4.03 TRASTUZUMAB DERUXTECAN,
Powder for I.V. infusion 100 mg,
Enhertu[®],
AstraZeneca Pty Ltd.**

23 Background

- 23.1 The resubmission requested a Section 100, Authority Required listing for trastuzumab deruxtecan (T-DXd; Enhertu[®]) for the treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer (BC) in a deferred population of patients who (i) have progressed following a prior HER2 directed therapy for metastatic disease, or relapsed during or within 6 months of receiving a HER2 directed adjuvant therapy; and (ii) would be prescribed T-DXd in a third and later line setting for metastatic disease.
- 23.2 At the March 2023 PBAC meeting, the PBAC deferred their decision regarding the requested listing for patients prescribed T-DXd in a third and later line setting. This was specifically relevant to patients who are currently on treatment with second line (2L) or 3L trastuzumab and would be treated with third or later line (3L+) T-DXd (paragraph 19.8).
- 23.3 The resubmission provided further information following the deferral and sought to address the PBAC's concerns from its March 2023 meeting. Table 33 summarises how the resubmission addressed the relevant issues.

Table 33: Summary of changes made in the resubmission

PBAC PSD recommended change March 2023	Resubmission change July 2023	Addressed?
Requested listing		
The requested restriction should incorporate (i) the patient groups recommended in March 2023 (patients who have received up to 2 prior lines of HER2 directed therapy for metastatic disease, or patients who have relapsed during or within 6 months of receiving a HER2 directed adjuvant therapy) (paragraph 19.2); and (ii) the patient group deferred in March 2023 (patients who would receive T-DXd in a third and later line setting who are currently on treatment with trastuzumab monotherapy) (paragraph 19.8).	The resubmission proposed that the restriction considered at the July 2022 meeting would incorporate all patient groups.	Yes.
Financial estimates		
The financial estimates should be adjusted to include a revised eligible patient population and revised duration of therapy for those who would receive T-DXd in a third and later line setting and are currently on treatment with trastuzumab monotherapy (paragraph 19.8).	The resubmission updated patient numbers and financial estimates based on the PBAC's advice that these latter line patients would be less likely to undergo treatment with T-DXd at the same rate as earlier line patients due to toxicity concerns compared with staying on trastuzumab monotherapy.	Yes.
Risk sharing arrangements		
Assuming that the financial estimates for the deferred population are acceptable to the PBAC, the RSA should incorporate financial estimates for all patient groups, noting that a [REDACTED] % rebate would be appropriate for use exceeding the financial caps (paragraph 19.7)	The resubmission proposed the additional (deferred) population be included in the same RSA with the same terms as that recommended in March 2023.	Yes.

PSD = public summary document; RSA = risk sharing arrangement; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

24 Requested listing

- 24.1 The PBAC considered in March 2023 that it would be clinically appropriate for T-DXd to be used in a third and later line setting (paragraph 19.8). The intention of the resubmission was to propose a single restriction that could incorporate all patients for whom the PBAC identified as clinically appropriate for T-DXd treatment.
- 24.2 The resubmission stated that the restriction proposed in the first submission for trastuzumab deruxtecan (July 2022) would suitably provide access to treatment with T-DXd by incorporating both:
- (i) the patient groups recommended at the March 2023 meeting:
 - those who have received up to 2 prior lines of HER2 directed therapy for metastatic disease, or patients who have relapsed during or within 6 months of receiving a HER2 directed adjuvant therapy.
 - (ii) the patient group deferred at the March 2023 meeting:

- those who would receive T-DXd in a third and later line setting.

The relevant clinical criteria included in the Public Summary Document from the July 2022 consideration was:

The condition must have progressed following treatment with at least one prior HER2 directed regimens for metastatic breast cancer OR

The condition must have progressed during or within 6 months following adjuvant treatment with a HER2 directed therapy.

- 24.3 The resubmission noted that the proposed restriction wording for T-DXd is different to that for the comparator, trastuzumab emtansine (T-DM1). The relevant clinical restriction criteria for T-DM1 specifies patients must have “progressed following treatment with pertuzumab and trastuzumab in combination” OR “progressed during or within 6 months of completing adjuvant therapy with trastuzumab.” The resubmission noted that the pivotal T-DXd Destiny Breast 03 (DB03) study required patients to have received prior trastuzumab and a taxane in the metastatic setting +/-pertuzumab, and that approximately 40% of patients in the trial had not received pertuzumab prior to being randomised to receive T-DXd. The resubmission stated that the restriction criteria for T-DXd should not specify pertuzumab as a necessary prior therapy because patients who do not receive pertuzumab in 1L will not be eligible to receive either TDM1 or T-DXd in 2L, despite DB03 demonstrating superior efficacy and cost effectiveness of T-DXd in a mixed prior pertuzumab population.

For more detail on PBAC’s view, see section 26 PBAC outcome.

25 Consideration of the evidence

Estimated PBS usage & financial implications

- 25.1 As a resubmission to provide further information addressing the previous deferral, the estimated utilisation and financial implications have not been independently evaluated.
- 25.2 At the March 2023 meeting, the PBAC considered that there were residual issues associated with the estimate for the potential number of 3L+ T-DXd patients from prevalent patients currently on treatment with trastuzumab monotherapy, and deferred its decision regarding the inclusion of these patients in its recommendation. The PBAC considered the submission made unrealistic assumptions about the number of 3L+ line patients who would be fit enough to receive T-DXd and their mean time-on-treatment, and therefore the number of scripts in this group was overestimated. The PBAC considered that the financial estimates should be adjusted to include a revised eligible patient population and revised duration of therapy for this patient group (paragraph 19.8).

- 25.3 Table 34 shows the estimated number of patients in the 2L+ trastuzumab monotherapy prevalent population who may switch to T-DXd in 3L+ over the current and previous considerations. The financial estimates in both the December 2022 and February 2023 resubmissions estimated this prevalent population in Year 1 of PBS listing to be 500 to < 5,000 patients (derived from prevalence data supplied to AZ by DUSC Secretariat in 2022). Applying an Eastern Cooperative Oncology Group (ECOG) score of 0-1 for 70% of patients reduced this estimate to 500 to < 5,000 patients in Year 1. The February 2023 resubmission applied a further 1% reduction to this number to acknowledge uncertainty in uptake, further reducing the estimate to 500 to < 5,000 patients in Year 1. Acknowledging the PBAC's view that these later line patients are less likely to undergo treatment with T-DXd at the same rate as earlier line patients due to toxicity concerns compared with staying on trastuzumab monotherapy, the estimate was reduced from 500 to < 5,000 to 500 to < 5,000 patients in Year 1.

Table 34: Estimated number of patients for 2L+ trastuzumab monotherapy patients switching to T-DXd in 3L+

Assumptions / Data Source	Patients
December 2022 consideration	
Prevalent population of patients currently receiving treatment with trastuzumab monotherapy in 2L+ projected from data provided by DoH	1 ^a
Patients with ECOG 0-1 70%	1 ¹
March 2023 consideration	
Prevalent population of patients currently receiving treatment with trastuzumab monotherapy in 2L+ projected from data provided by DoH	1 ^a
Patients with ECOG 0-1 70%	1 ¹
1% reduction to account for uncertainty in uptake	1 ¹
July 2023 consideration	
A further 1% ^b reduction from 1 ¹ to account for uncertainty in uptake & toxicity	1 ¹

DoH = Department of Health; ECOG = Eastern Cooperative Oncology Group; 2L+ = second or later line; 3L+ = third or later line.

^a This number was stated to be 500 to < 5,000 in the resubmission, but it has been corrected to 500 to < 5,000 by the Secretariat.

^b This proportion was stated to be 1% in the resubmission, but it has been corrected to 1% by the Secretariat.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

- 25.4 The duration of therapy for this deferred patient population was derived from the final analysis of the DESTINY Breast-01 study (Saura et al 2021)¹² showing a median progression free survival (PFS) of 19.4 months after a median 26.5 months duration of follow-up (paragraph 6.13). The DESTINY Breast-02 study is a phase 3 RCT in the same population comparing the efficacy and safety of T-DXd with physicians choice for patients who have received at least two prior lines of therapy in the metastatic setting. The most recent data analysis from this study showed median PFS of 17.8 months (Fabrice et al 2023) for subjects receiving T-DXd at a median duration of follow-up of 21.5 months. The resubmission stated that the results from DB01 (19.4 months) were chosen as the duration of therapy as it was derived from more mature data. This

¹² Trastuzumab Deruxtecan (T-DXd) in Patients with HER2-Positive Metastatic Breast Cancer: Updated Survival Results from a Phase 2 Trial (DESTINY-Breast01), Poster at the European Society for Medical Oncology (ESMO) 2021 Annual Meeting; September 16-21, 2021.

compares to a duration of therapy of 29.01 months for the primary incident pool of patients recommended in March 2023.

- 25.5 The financial estimates presented in the July 2023 resubmission used an effective price/vial of \$¹, consistent with the price per vial for T-DXd considered cost effective by the PBAC at the time of the recommendation in March 2023. This T-DXd price does not incorporate the cost effective price for T-DM1 as managed through a RSA (paragraph 19.5).
- 25.6 Table 35 shows the estimated number of patients and the effective cost of T-DXd to the PBS/RPBS in the patient population switching to T-DXd from 2L+ trastuzumab monotherapy. The total estimated net cost to the R/PBS for this additional population is \$40 million to < \$50 million over six years. This compares to a net financial impact of \$300 million to < \$400 million over six years for the primary incident pool of patients recommended in March 2023 (also calculated at a price/vial of \$¹) (Table 30).

Table 35: Estimated T-DXd patients and effective cost across the first six years of listing in (i) the patient population switching to T-DXd from 2L+ trastuzumab monotherapy and (ii) the recommended primary pool of patients

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
(i) July 2023 resubmission for deferred population: EMP = \$²							
Patients	¹	²	²	²	²	²	¹
Net T-DXd cost^a	\$ ³	\$ ³	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁵
Substituted medicines^a	\$ ⁶	\$ ⁶	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁷
Net financial impact^a	\$ ⁶	\$ ⁷	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁸
(ii) March 2023 resubmission for the primary incident pool of patients (recommended): EMP = \$²							
Net financial impact^a	\$ ⁸	\$ ⁵	\$ ⁵	\$ ⁹	\$ ⁹	\$ ⁹	\$ ¹⁰
Total cost for deferred and primary incident pool of patients: EMP = \$²							
Net financial impact^a	\$ ¹¹	\$ ¹²	\$ ¹³	\$ ⁹	\$ ⁹	\$ ⁹	\$ ¹⁴

Source: Enhertu (T-DXd)_UCM_AZ_Update_2Lplus [Worksheet 5.Impact-net]

EMP = ex-manufacturer price; T-DXd = trastuzumab deruxtecan.

^a Effective price minus patient co-payment

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ \$30 million to < \$40 million

⁴ \$0 to < \$10 million

⁵ \$70 million to < \$80 million

⁶ \$10 million to < \$20 million

⁷ \$20 million to < \$30 million

⁸ \$40 million to < \$50 million

⁹ \$60 million to < \$70 million

¹⁰ \$300 million to < \$400 million

¹¹ \$50 million to < \$60 million

¹² \$100 million to < \$200 million

¹³ \$80 million to < \$90 million

¹⁴ \$400 million to < \$500 million

Financial Management – Risk Sharing Arrangements

- 25.7 The resubmission proposed that the additional population requested in the resubmission (switching to T-DXd from 2L+ trastuzumab monotherapy) be included in the same RSA with the same terms as the population recommended at the March 2023 meeting (the primary incident pool of patients).

For more detail on PBAC's view, see section 26 PBAC outcome.

26 PBAC outcome

- 26.1 The PBAC recommended the listing of trastuzumab deruxtecan (T-DXd) for the treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer for patients who have progressed following treatment with at least one prior HER2 directed regimen/s for metastatic disease, or relapsed during or within 6 months of receiving HER2 directed adjuvant therapy. The recommendation pertained to the deferred population from the March 2023 consideration (those who would receive T-DXd in a third and later line setting), which was additional to the recommended population at the March meeting (those who have received up to 2 prior lines of HER2 directed therapy for metastatic disease, or patients who have relapsed during or within 6 months of receiving a HER2 directed adjuvant therapy), to allow for a single restriction that includes all patients for whom the PBAC identified in March 2023 as clinically appropriate for treatment with T-DXd.
- 26.2 The PBAC considered that the restriction for the overall patient group should be consistent with the restriction proposed by the Sponsor at the July 2022 meeting, where the relevant clinical criteria stated that: "The condition must have progressed following treatment with at least one prior HER2 directed regimens for metastatic breast cancer OR The condition must have progressed during or within 6 months following adjuvant treatment with a HER2 directed therapy." The PBAC considered that the same parameters should apply to the wider listing as was agreed in March 2023; that is, an Authority Required (telephone/online) listing should be available under the Section 100 (Efficient Funding of Chemotherapy) schedule with a single treatment phase listing and patients are required to have a WHO performance status of 0 or 1.
- 26.3 The PBAC recalled that if the average price of T-DM1 is managed through a RSA, the agreed cost-effective price for T-DM1 should be incorporated into the economic model for T-DXd and a price reduction would be required for T-DXd to be considered cost-effective (paragraph 19.5). For the purposes of revising the financial implications for the July 2023 consideration, the resubmission used a price of \$1 per vial, which was the price proposed in the March 2023 submission. The PBAC considered that similar arrangements to those that are negotiated for the March 2023 recommended primary incident pool of patients (incorporating application of the T-DM1 RSA parameters) should also apply to this population.

- 26.4 The PBAC accepted that the resubmission largely addressed its concerns raised at the March 2023 consideration in terms of revising the eligible patient population and treatment duration for patients switching to T-DXd treatment from 2L+ trastuzumab monotherapy. The PBAC considered that the proposed 1% reduction from the March 2023 estimate of 500 to < 5,000 patients to 500 to < 5,000 patients in the resubmission adequately reflected the PBAC's view that these later line patients would be less likely to undergo treatment with T-DXd at the same rate as earlier line patients due to (i) fitness to commence treatment with T-DXd; and (ii) toxicity concerns. While the PBAC considered the claimed duration of therapy of 19.4 months to be uncertain, it accepted this estimate in the context of the reduced patient pool and it being lower than the duration for the primary incident pool of patients.
- 26.5 The PBAC considered that uncertainties in the financial estimates and the potential for use in a broader patient population where the use may not be cost-effective should be managed by a RSA. The PBAC considered that the financial caps should incorporate both the primary incident pool of patients approved in March 2023 and the currently recommended patient population switching to T-DXd from 2L+ trastuzumab, and reiterated that a 1% rebate would be appropriate for use exceeding the caps.
- 26.6 The PBAC recommended that T-DXd should not be treated as interchangeable with any other drugs.
- 26.7 The PBAC advised that T-DXd is not suitable for prescribing by nurse practitioners. The PBAC noted that existing HER2 directed therapies are not available for nurse prescribing.
- 26.8 The PBAC recommended that the Early Supply Rule should not apply to T-DXd. The PBAC noted that the Early Supply Rule does not apply to T-DM1.
- 26.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for T-DXd:
 - d) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over the nominated comparator in terms of overall survival in the metastatic and adjuvant breast cancer populations;
 - e) The treatment is expected to address a high and urgent unmet clinical need as patients with HER2 positive breast cancer carry a heavy burden of disease despite the current medicines available;
 - f) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 26.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

27 Recommended listing

27.1 Add new medicinal product as follows:

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRASTUZUMAB DERUXTECAN Injection	NEW (Public) NEW (Private) MP	675 mg	8
Available brands			
Enhertu (trastuzumab deruxtecan 100 mg injection, 1 vial)			
Restriction Summary [new 1] / Treatment of Concept: [new 1.1]: Authority Required			
	Prescriber type: Medical Practitioners		
	Restriction type: Authority Required (telephone/online PBS Authorities system)		
	Episodicity: [blank]		
	Severity: Metastatic (Stage IV)		
	Condition: HER2 positive breast cancer		
	Indication: Metastatic (Stage IV) HER2 positive breast cancer		
	Clinical criteria:		
	Patient must have evidence of human epidermal growth factor (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) in either the primary tumour/a metastatic lesion – establish this finding once only with the first PBS-prescription		
	AND		
	Clinical criteria:		
	The condition must have progressed following treatment with at least one prior HER2 directed regimen for metastatic breast cancer; OR		
	The condition must have, at the time of treatment initiation with this drug, progressed during/within 6 months following adjuvant treatment with a HER2 directed therapy		
	AND		
	Clinical criteria:		
	Patient must have, at the time of initiating treatment with this drug, a WHO performance status no higher than 1.		
	AND		
	Clinical criteria:		
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.		
	AND		
	Clinical criteria:		
	The treatment must not be prescribed where any of the following is present: (i) left ventricular ejection fraction of less than 50%, (ii) symptomatic heart failure; confirm cardiac function testing for the first PBS-prescription only		

	Treatment criteria:
	Patient must be undergoing initial treatment with this drug – the following are true: (i) this is the first prescription for this drug, (ii) this prescription seeks no more than 3 repeat prescriptions; or
	Patient must be undergoing continuing treatment with drug – the following are true: (i) there has been an absence of further disease progression whilst on active treatment with this drug, (ii) this prescription does not seek to re-treat after disease progression, (iii) this prescription seeks no more than 8 repeat prescriptions
	Prescribing Instructions: Confirm that the following information is documented/retained in the patient's medical records once only with the first PBS prescription: 1) Evidence of HER2 gene amplification (evidence obtained in relation to past PBS treatment is acceptable), 2) Details of prior HER2 directed drug regimens prescribed for the patient 3) Cardiac function test results (evidence obtained in relation to past PBS treatment is acceptable)
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
	Administrative Advice: Increased maximum amounts can be requested where a patient's weight is greater than 125 kg.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

28 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

29 Sponsor's Comment

The sponsor had no comment.